IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Akira Nishiyama et al.
Serial No. 09/990,389 Group Art Unit 1626
Filed November 23, 2001 Examiner SMALL, ANDREA D SOUZA
For : PHENOXYPROPYLAMINE COMPOUNDS

TRANSLATOR'S DECLARATION

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of the certified copy of Japanese Patent Application No. 277384/1999 filed on September 29, 1999; and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 11th day of July, 2003.

Ritsuko Arimura

Ritsuko Arimura

(Translation)

P A T E N T O F F I C E

J A P A N E S E G O V E R N M E N T

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application : September 29, 1999

Application Number : 277384/1999

Applicant(s) : Welfide Corporation

June 23, 2000

Commissioner, Patent Office
Takahiko Kondo
Certificate No. 2000-3047126

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【Telephone Number】 06-6201-1908
【Priority Claim Based on Prior Application】
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【Official Fee】

【Deposit Ledger Number】 013114

【Payment Amount】 ¥21,000

【List of the Annexed Documents】

【Document】 Specification One copy

【Document】 Abstract One copy

【Number of General Power of Attorney】 9000146

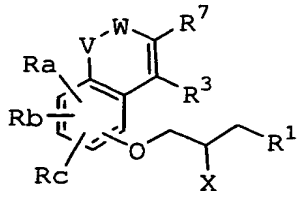
【Proof】 Requested

【Document】 Specification

【Title of the Invention】 Aromatic heterocyclic compound

【What is Claimed is】

【Claim 1】 A compound of the formula (I)

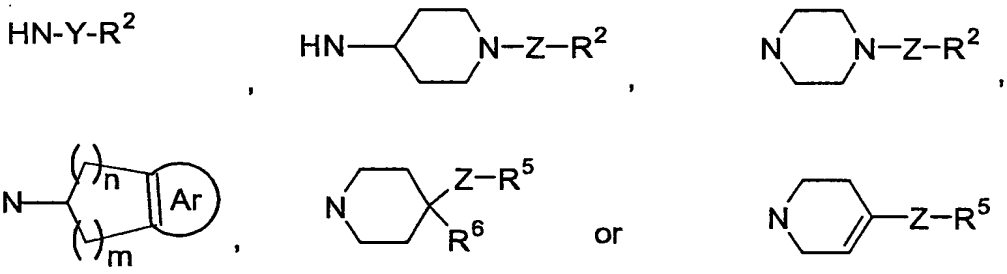


(I)

wherein each symbol in the formula means as follows:

X is a hydrogen atom, a hydroxy group, a C_1–C_8 alkoxy group or an acyloxy group;

R^1 is a group of the following formula



wherein

Y is optionally substituted C_3–C_8 cycloalkyl or optionally branched C_1–C_8 alkylene,

m and n are each independently 0, 1 or 2,

Ar is optionally substituted benzene or naphthalene,

R^2 is optionally substituted aryl group or optionally substituted aromatic heterocyclic group,

R^5 is optionally substituted aryl group or optionally substituted aromatic heterocyclic group,

Z is void or CH_2, and

R^6 is hydrogen atom, hydroxy group or C_1–C_8 alkoxy group;

R^3 is a hydrogen atom, C_1–C_{18} alkyl or halogen;

V is CH_2, O, S or the formula N–R^4

wherein R^4 is hydrogen, C_1–C_{18} alkyl group or optionally

substituted aralkyl;

W is void, CH_2 or CO; or

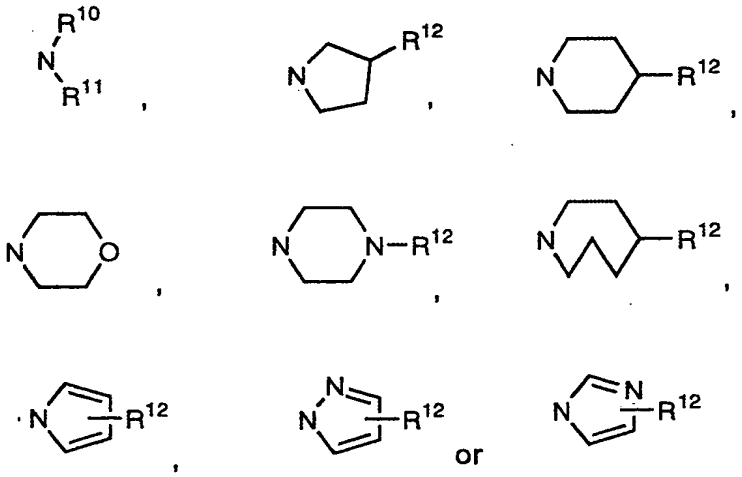
V and W are each a hydrogen atom without direct bonding;

R^7 is a C_1-C_4 hydroxyalkyl group, an acyl group, an optionally substituted saturated or unsaturated heterocyclic group, an optionally substituted fused heterocyclic group or the formula $-Q-R^9$

wherein

Q is CO, CS, CH_2 or SO_2, and

R^9 is a group of the following formula



wherein R^{10} and R^{11} are each independently hydrogen atom, C_1-C_{18} alkyl group, optionally substituted aryl or aralkyl, R^{12} is hydrogen atom, optionally substituted aryl group, C_1-C_{18} alkyl group, C_1-C_8 alkoxy group or acyl group; and

Ra, Rb and Rc are the same or different and each represents a hydrogen atom, a C_1-C_{18} alkyl group, a hydroxy group, a C_1-C_8 alkoxy group, a halogen atom, an acyl group, a nitro group or an amino group;

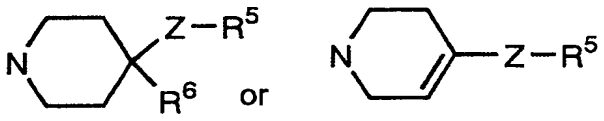
provided that when V and W are not directly bonded and V and W are both hydrogen atoms, R^7 should not be a group of the formula $-CO-R^9$;

an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

【Claim 2】 The compound of claim 1, which is represented by the formula (I) wherein each symbol in the formula means as follows:

X is a hydroxy group;

R^1 is a group of the following formula



wherein

R^5 is optionally substituted phenyl group or naphthyl group,

Z is void, and

R^6 is hydrogen atom;

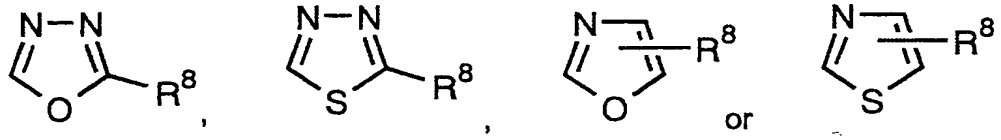
R^3 is a hydrogen atom or a C_1-C_4 alkyl group;

V is CH_2, O, S or N-R^4

wherein R^4 is hydrogen atom, C_1-C_6 lower alkyl group or optionally substituted aralkyl group;

W is void;

R^7 is a group of the following formula

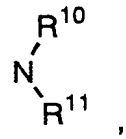


wherein

R^8 is hydrogen, phenyl group, C_1-C_4 alkyl group, or C_1-C_2 halogenated alkyl group,

or R^7 represents the formula -CO-R^9, and

R^9 is a group of the following formula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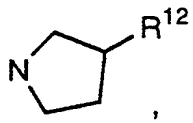
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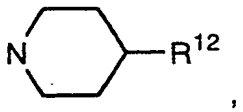
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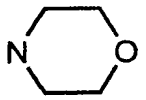
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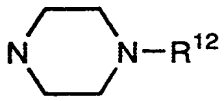
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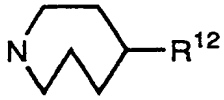


wherein R^{10} and R^{11} are each independently hydrogen atom, C_1-C_{18} alkyl group, optionally substituted aryl group or aralkyl group, and R^{12} is hydrogen atom, optionally substituted aryl group, C_1-C_{18} alkyl group, C_1-C_8 alkoxy group or acyl group; and

Ra, Rb and Rc are each a hydrogen atom;

an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

【Claim 3】 The compound of claim 1, which is selected from

1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-benzo(b)furan-2-ylcarbonyl)pyrrolidine,

4-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylcarbonyl)morpholine,

4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)furan-2-carboxamide,

1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)thiophen-2-ylcarbonyl)pyrrolidine,

4-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)thiophen-2-ylcarbonyl)morpholine,

4-(2-hydroxy-3-(4-(naphthalen-1-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide,

4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide,

4-(7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylcarbonyl)morpholine,

7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)furan-2-carboxamide,

4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethyl-1H-indole-2-carboxamide,

4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethyl-1-methyl-indole-2-carboxamide,

1-(2-(5-methyl-1,2,4-oxadiazol-3-yl)-benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

1-(2-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indole-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

1-(2-(3-methyl-1,2,4-oxadiazol-5-yl)-benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

1-(2-(5-methyloxazol-2-yl)-benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

3-(4-(3,4-dichlorophenyl)piperidino)-1-(2-(5-methyloxazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol,

1-(4-(3,4-dichlorophenyl)piperidino)-3-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol, and

3-(4-(3,4-dimethylphenyl)piperidino)-1-(2-(5-ethyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol,

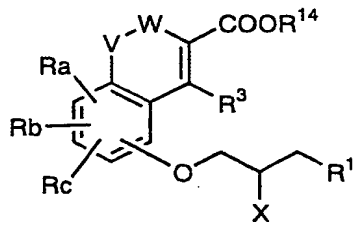
an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

【Claim 4】 A pharmaceutical agent comprising a compound of claim 1, an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

【Claim 5】 The pharmaceutical agent of claim 4, which is an agent for the treatment of depression improving depression symptom in a mammal inclusive of a human.

【Claim 6】 A pharmaceutical composition comprising a compound having anti-depression action selected from a compound of claim 1, an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof, and a pharmaceutically acceptable carrier.

【Claim 7】 A compound of the formula (II)

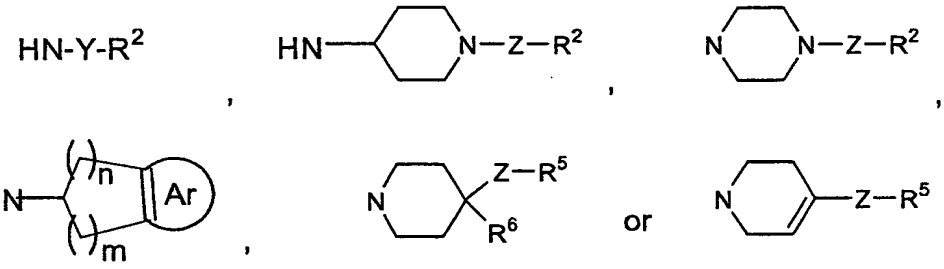


(II)

wherein each symbol in the formula means as follows:

X is a hydrogen atom, a hydroxy group, a C_1–C_8 alkoxy group or an acyloxy group;

R^1 is a group of the following formula



wherein

Y is optionally substituted C_3–C_8 cycloalkyl or optionally branched C_1–C_8 alkylene,

m and n are each independently 0, 1 or 2,

Ar is optionally substituted benzene or naphthalene,

R^2 is optionally substituted aryl group or optionally substituted aromatic heterocyclic group,

R^5 is optionally substituted aryl group or optionally substituted aromatic heterocyclic group,

Z is void or CH_2, and

R^6 is hydrogen atom, hydroxy group or C_1-C_8 alkoxy group;

R^3 is a hydrogen atom, a C_1-C_{18} alkyl group or a halogen atom;

V is CH_2, O, S or the formula N-R^4

wherein

R^4 is hydrogen, C_1-C_{18} alkyl group or optionally substituted aralkyl group;

W is void, CH_2 or CO; or

V and W are each a hydrogen atom without direct bonding;

R^{14} is a hydrogen atom or a C_1-C_4 alkyl; and

Ra, Rb and Rc are same or different, each represents a hydrogen atom, a C_1-C_{18} alkyl group, a hydroxy group, a C_1-C_8 alkoxy group,

a halogen atom, an acyl group, a nitro group or an amino group; an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

【Detailed Descripition of the Invention】

【Technical Field to which the Invention Pertains】

The present invention relates to a compound that acts on 5-hydroxytryptamine (5-HT) neurotransmission. More particularly, the present invention relates to a novel phenoxypropylamine derivative having selective affinity for and simultaneous antagonistic activity against a 5-hydroxytryptamine 1A ($5\text{-}HT_{1A}$) receptor in the central nervous system, as well as a 5-HT reuptake inhibitory activity, which is useful as a pharmaceutical agent, and to a therapeutic agent for depression and the like, which contains this compound. 5-Hydroxytryptamine (5-HT) is also known as "serotonin".

【Prior Art】

As a compound having an antagonistic activity against $5\text{-}HT_{1A}$ receptor as well as an inhibitory activity on the reuptake of 5-HT, there are known, for example, 1-(4-indolyloxy)-3-(4-(3,4-methylenedioxyphenyl)piperidino)-2-propanol derivative (EP

0722941), 4-(4-fluorophenyl)-1-(6-methylaminoindan-1-ylmethyl)piperidine derivative (WO 95/33721), 3,6-dihydro-N-methyl-N-(5-chloro-2-pyridyl)-4-(1-naphthalenyl)-1-(2H)pyridine propanamine derivative (US Patent No. 5472966), 3-(5-chlorobenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-b]thiazol derivative (WO 97/02269), S-(-)-N-(2-(3-(2-naphthyl)-pyrrolidino)ethyl)-N-(2-pyridyl)cyclohexanecarboxamide derivative (WO 97/40038), (R)-3-(N-cyclopentyl-N-n-propylamino)-8-fluoro-5-(N-methylcarbamoyl)-3,4-dihydro-2H-1-benzopyran derivative (WO 96/33710), 3-(2-(4-methylpiperazin-1-yl)benzylidene)-1,3-dihydroindol-2-one derivative (WO 97/36867), 1-(4-indolyloxy)-3-[4-hydroxy-4-(2-naphthyl)piperidino]propan-2-ol derivative (WO 97/48698) and the like.

JP-A-62-116557 discloses substituted benzyllactams, such as 2-hydroxy-1-[2-(2-oxo-4-pyrrolidinylmethyl)phenoxy]-3-(4-diphenylmethyl-piperazin-1-yl)propane and the like, which have a binding ability with a serotonin receptor and a muscarinic acetylcholine receptor, and which can be used for the treatment of senile dementia, Alzheimer's disease, cerebrovascular dementia and the like.

【Problems to be Solved by the Invention】

Various diseases of the central nervous system (e.g., depression, anxiety) are considered to be caused by disorders of noradrenalin (NA) and 5-hydroxytryptamine (5-HT), which are neurotransmitters. Accordingly, augmentation of 5-HTergic neurotransmission is considered to mainly influence depressive mood and anxious, whereas augmentation of noradrenergic neurotransmission is considered to influence retardation in depressive patients. The pharmaceutical agents, such as imipramine, desipramine and the like, which are most frequently used for the treatment of depression, are considered to act on depressive patients by improving neurotransmission of one or both of these.

The activity of 5-HT is considered to relate to a number

of various types of psychiatric disorders. In addition, 5-HT has been considered to be responsible for various conditions (e.g., eating disorder, gastrointestinal injury, control of cardiovascular system and sexual behavior). However, conventional antidepressants, such as imipramine, desipramine and the like, are defective in that they require 3 - 4 weeks or even longer time for the expression of an anti-depressive effect, which poses clinical problems.

A combined use of various pharmaceutical agents has been considered in an attempt to accelerate expression of effects of antidepressants or to increase their efficacy (Journal of Clinical Psychiatry, Vol. 57; Suppliment 7; pp 25-31). Therein, a noticeably shortened time for clinical expression of the effect by concurrent use of a selective serotonin (5-HT) reuptake inhibitor (SSRI) and a 5-HT_{1A} antagonist, pindolol, has been reported (Journal of Clinical Psychopharmacology, Vol. 17, No. 6, pp. 446-450). It is known that the amount of 5-HT release in the brain does not increase much by SSRI alone, but when combined with a 5-HT_{1A} antagonist, the amount increases markedly (Neurochemical Research, Vol. 21, No. 5, 1996, pp. 557-562). Under such circumstances, the "5-HT enhancement hypothesis" was proposed with regard to the expression of the action of antidepressants by Blier and de Montigny (Trends in Pharmacological Sciences, 1994, vol. 15, pp. 220-226). The 5-HT enhancement hypothesis means that the effector mechanism of antidepressant rests in the enhancement of 5-HT release at a terminal. It is based on the understanding that the conventional antidepressants decrease the 5-HT release by single administration, but increase the 5-HT release and express an anti-depressive effect only when they are administered consecutively. From those mentioned above, it is expected that a drug that promotes 5-HT release in the brain from the first can be a rapid onset antidepressant. In other words, a compound concurrently having a serotonin reuptake

inhibitory action and a 5-HT_{1A} antagonistic action is considered to be an antidepressant showing quick expression of an anti-depressive effect, namely, a rapid onset antidepressant.

It is an object of the present invention to find a subgroup of 5-hydroxytryptamine (5-HT) receptor, namely, a compound simultaneously having selective affinity for and antagonistic activity against 5-HT_{1A} receptor in the central nervous system in mammals inclusive of human, which compound also having a 5-HT reuptake inhibitory activity.

It is therefore an object of the present invention to provide a compound that expresses an anti-depressive effect quickly, which is a so-called rapid onset antidepressant, and a compound useful for the treatment of 5-HT mediated diseases in the central nervous system, such as schizophrenia, anxiety neurosis, obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, seasonal emotional disorder, Anorexia Nervosa, Bulimia Nervosa, nocturnal enuresis, children's hyperlocomotion, post-traumatic stress disorder(PTSD), senile dementia, hemicrania, stroke, Alzheimer's disease, recognition disorder, hypertension, gastrointestinal injury, feeding disorders, abnormal body temperature regulation, sexual disorder and pain, as well as for the treatment of abnormality in the cardiovascular system.

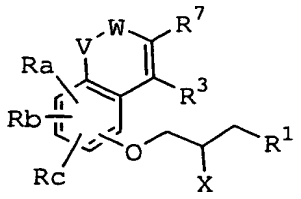
【Means of Solving the Problems】

The present inventors have conducted intensive studies, and as a result, found that a novel aromatic heterocyclic compound of the formula (I), an optical isomer thereof and a pharmaceutically acceptable salt thereof have a inhibitory action for serotonin reuptake and a 5-HT_{1A} antagonist action, and can be a useful pharmaceutical agent that meets the above-mentioned objects, which resulted in the completion of the present invention.

Accordingly, the present invention provides the

following.

1. A compound of the formula (I)

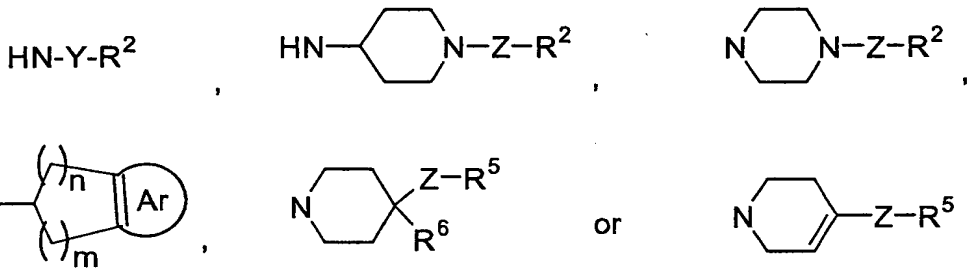


(I)

wherein each symbol in the formula means as follows:

X is a hydrogen atom, a hydroxy group, a C_1–C_8 alkoxy group or an acyloxy group;

R^1 is a group of the following formula



wherein

Y is optionally substituted C_3–C_8 cycloalkyl or optionally branched C_1–C_8 alkylene,

m and n are each independently 0, 1 or 2,

Ar is optionally substituted benzene or naphthalene,

R^2 is optionally substituted aryl group or optionally substituted aromatic heterocyclic group,

R^5 is optionally substituted aryl group or optionally substituted aromatic heterocyclic group,

Z is void or CH_2, and

R^6 is hydrogen atom, hydroxy group or C_1–C_8 alkoxy group;

R^3 is a hydrogen atom, C_1–C_{18} alkyl or halogen;

V is CH_2, O, S or the formula N–R^4

wherein R^4 is hydrogen, C_1–C_{18} alkyl group or optionally substituted aralkyl;

W is void, CH_2 or CO; or

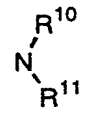
V and W are each a hydrogen atom without direct bonding;

R^7 is a C_1–C_4 hydroxyalkyl group, an acyl group, an optionally substituted saturated or unsaturated heterocyclic group, an optionally substituted fused heterocyclic group or the formula $-Q-R^9$

wherein

Q is CO, CS, CH_2 or SO_2, and

R^9 is a group of the following formula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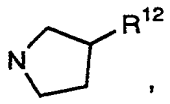
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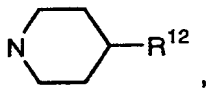
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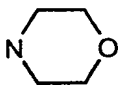
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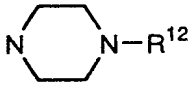
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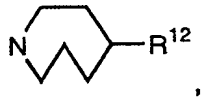
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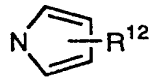
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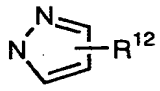
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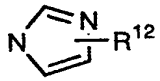


wherein R^{10} and R^{11} are each independently hydrogen atom, C_1–C_{18} alkyl group, optionally substituted aryl or aralkyl, R^{12} is hydrogen atom, optionally substituted aryl group, C_1–C_{18} alkyl group, C_1–C_8 alkoxy group or acyl group; and

Ra, Rb and Rc are the same or different and each represents a hydrogen atom, a C_1–C_{18} alkyl group, a hydroxy group, a C_1–C_8 alkoxy group, a halogen atom, an acyl group, a nitro group or an amino group;

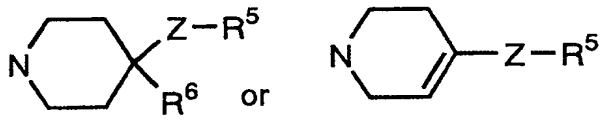
provided that when V and W are not directly bonded and V and W are both hydrogen atoms, R^7 should not be a group of the formula $-CO-R^9$;

an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

2. The compound of (1) above, which is represented by the formula (I) wherein each symbol in the formula means as follows:

X is a hydroxy group;

R^1 is a group of the following formula



wherein

R^5 is optionally substituted phenyl group or naphthyl group,

Z is void, and

R^6 is hydrogen atom;

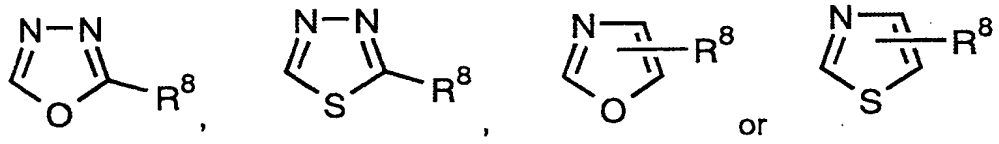
R^3 is a hydrogen atom or a C_1-C_4 alkyl group;

V is CH_2, O, S or N-R^4

wherein R^4 is hydrogen atom, C_1-C_6 lower alkyl group or optionally substituted aralkyl group;

W is void;

R^7 is a group of the following formula

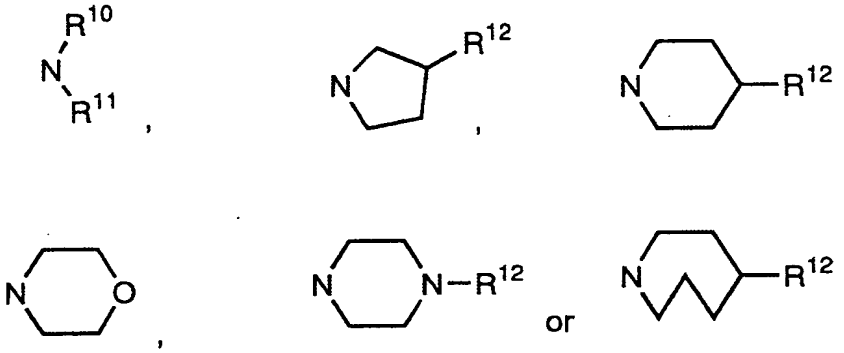


wherein

R^8 is hydrogen, phenyl group, C_1-C_4 alkyl group, or C_1-C_2 halogenated alkyl group,

or R^7 represents the formula -CO-R^9, and

R^9 is a group of the following formula



wherein R^{10} and R^{11} are each independently hydrogen atom, C_1-C_{18} alkyl group, optionally substituted aryl group or aralkyl group, and R^{12} is hydrogen atom, optionally substituted aryl group, C_1-C_{18} alkyl group, C_1-C_8 alkoxy group or acyl group; and

Ra, Rb and Rc are each a hydrogen atom;

an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

3. The compound of (1) above, which is selected from

(1) 1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylcarbonyl)pyrrolidine,

(2) 4-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylcarbonyl)morpholine,

(4) 4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)furan-2-carboxamide,

(12) 1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)thiophen-2-ylcarbonyl)pyrrolidine,

(13) 4-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)thiophen-2-ylcarbonyl)morpholine,

(15) 4-(2-hydroxy-3-(4-(naphthalen-1-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide,

(17) 4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide,

(20) 4-(7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylcarbonyl)morpholine,

(21) 7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)furan-2-carboxamide,

(27) 4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethyl-1H-indole-2-carboxamide,

(30) 4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethyl-1-methyl-indole-2-carboxamide,

(35) 1-(2-(5-methyl-1,2,4-oxadiazol-3-yl)-benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

(37) 1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

(38) 1-(2-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)-benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

(39) 1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

(42) 1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indole-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

(44) 1-(2-(3-methyl-1,2,4-oxadiazol-5-yl-benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

(48) 1-(2-(5-methyloxazol-2-yl)-benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol,

(81) 3-(4-(3,4-dichlorophenyl)piperidino)-1-(2-(5-methyloxazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol,

(88) 1-(4-(3,4-dichlorophenyl)piperidino)-3-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol, and

(93) 3-(4-(3,4-dimethylphenyl)piperidino)-1-(2-(5-ethyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol,

an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

4. A pharmaceutical agent comprising a compound of (1) above, an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

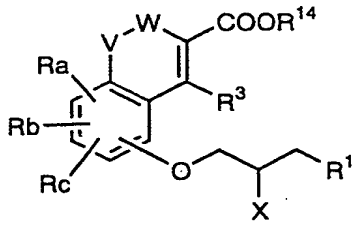
5. The pharmaceutical agent of (4) above, which is an agent for the treatment of depression improving depression symptom in

a mammal inclusive of a human.

6. A pharmaceutical composition comprising a compound having anti-depression action selected from a compound of (1) above, an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof, and a pharmaceutically acceptable carrier.

In addition, the present invention provides the following intermediate.

7. A compound of the formula (II)

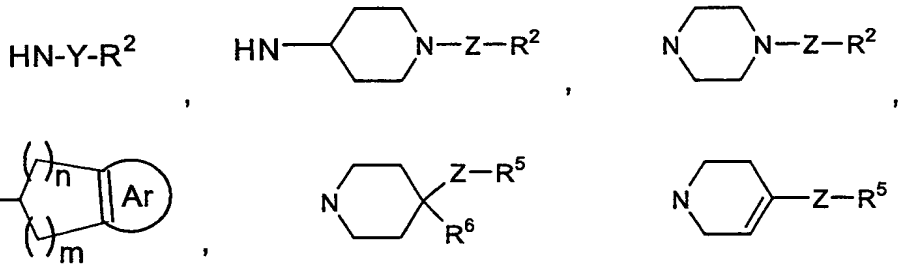


(II)

wherein each symbol in the formula means as follows:

X is a hydrogen atom, a hydroxy group, a C_1-C_8 alkoxy group or an acyloxy group;

R^1 is a group of the following formula



wherein

Y is optionally substituted C_3-C_8 cycloalkyl, or optionally branched C_1-C_8 alkylene,

m and n are each independently 0, 1 or 2,

Ar is optionally substituted benzene or naphthalene,

R^2 is optionally substituted aryl group or optionally substituted aromatic heterocyclic group,

R^5 is optionally substituted aryl group or optionally

substituted aromatic heterocyclic group,

Z is void or CH_2, and

R^6 is hydrogen atom, hydroxy group or C_1-C_8 alkoxy group;

R^3 is a hydrogen atom, a C_1-C_{18} alkyl group or a halogen atom;

V is CH_2, O, S or the formula N-R^4

wherein

R^4 is hydrogen, C_1-C_{18} alkyl group or optionally substituted aralkyl group;

W is void, CH_2 or CO; or

V and W are each a hydrogen atom without direct bonding;

R^{14} is a hydrogen atom or a C_1-C_4 alkyl; and

Ra, Rb and Rc are same or different, each represents a hydrogen atom, a C_1-C_{18} alkyl group, a hydroxy group, a C_1-C_8 alkoxy group,

a halogen atom, an acyl group, a nitro group or an amino group; an optically active compound thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

【Embodiment of the Invention】

The examples of each group in the formula (I) are shown in the following.

The acyloxy group at X is, for example, acetyl, propionyl, butyryl, benzoyl and the like.

Optionally substituted C_3-C_8 cycloalkyl at Y of R^1 includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The substituents include C_1-C_4 alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl tert-butyl and the like; C_1-C_8 alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy octyloxy and the like; hydroxyl, oxo, hydrogen and the like.

Optionally branched C_{1-8} alkylene at Y of R^1 includes methylene, ethylene, trimethylene, tetramethylene,

pentametylene, hexamethylene, heptamethylene, octamethylene, methylmethylene, dimethylmethylene, 1-methylethylene, 2-methylethylene, 1,1-dimethylethylene, 2,2-dimethylethylene, ethylmethylene, diethylmethylene, 1-ethylethylene, 2-ethylethylene, 1-methyltrimethylene, 1,1-dimethyltrimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 3-methyltrimethylene, 3,3-dimethyltrimethylene, 1-ethyltrimethylene, 2-ethyltrimethylene, 3-ethyltrimethylene and the like. Preferred is ethylene, trimethylene or tetramethylene.

The optionally substituted aryl group at R^2, R^5, R^{10}, R^{11} and R^{12} is, for example, phenyl, naphthyl and the like. In R^5, preferred are naphthyl (1-naphthyl, 2-naphthyl), 4-chloro-3-fluorophenyl, 3-chloro-4-trifluoromethylphenyl and 3,4-dimethylphenyl.

The optionally substituted aromatic heterocyclic group at R^2 and R^5 is, for example, pyridyl, furyl, thienyl, pyrimidinyl, indol-2-yl, benzo(b)thiophen-2-yl, benzo(b)furan-2-yl, 3,4-methylenedioxyphenyl and the like. The "substituent" represents one to three selected from halogen (e.g., fluorine, chlorine, bromine etc.), haloalkyl (e.g., fluoromethyl, difluoromethyl, trifluoromethyl etc.), C_1-C_4 alkyl (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.), C_1-C_8 alkoxy group (methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy etc.), hydroxy, nitro, cyano, amino, C_1-C_4 mono or dialkylamino (methylamino, dimethylamino, diethylamino, dipropylamino etc.), acyl (acetyl, propionyl, butyryl etc.), C_2-C_6 alkenyl (vinyl, 1-propenyl, 2-propenyl, 3-propenyl etc.), C_2-C_6 alkynyl (ethynyl, 1-propynyl, 2-propynyl etc.), phenyl, phenoxy, benzyloxy, C_1-C_4 alkyl-S(O)t-2, phenyl-S(O)t- wherein t is 0, 1 or 2, carbamoyl and N,N-dialkylcarbamoyl (N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl etc.).

The C_1-C_8 alkoxy group at X, R^6, R^{12}, Ra, Rb and Rc is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy, or octyloxy, with preference given to C_1-C_4 alkoxy, with particular preference given to methoxy.

The halogen at R^3, Ra, Rb and Rc is fluorine, chlorine, bromine or iodine, preferably fluorine.

The C_1-C_{18} alkyl group at R^3, R^4, R^{10}, R^{11}, R^{12}, Ra, Rb, and Rc is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl, decyl, hexadecyl, octadecyl or the like. Preffered is C_1-C_4 alkyl, particularly methyl or ethyl.

The C_1-C_4 alkyl group at R^8 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl or the like.

The acyl group at R^7, R^{12}, Ra, Rb and Rc is acetyl, propionyl, butyryl, pentanoyl, hexanoyl, benzoyl or the like, particularly preferably C_2-C_3 acyl group.

The optionally substituted aralkyl at R^4, R^{10}, and R^{11} is a group wherein C_1-C_4 chain alkyl is substituted by phenyl group. Examples thereof include benzyl, 2-phenylethyl, 1-phenylethyl, 1,1-dimethyl-2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl, 4-phenylbutyl, 3-phenylbutyl, 2-phenylbutyl, 1-phenylbutyl and the like, with preference given to benzyl. Examples of these substituents include halogen (e.g., fluorine, chlorine, bromine etc.), haloalkyl (fluoromethyl, difluoromethyl, trifluoromethyl etc.), C_1-C_4 alkyl (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.), C_1-C_8 alkoxy (methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy etc.), hydroxy, nitro, cyano, amino and the like.

The C_1-C_2 halogenated alkyl group at R^8 is chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or the like, preferably

trichloromethyl and trifluoromethyl.

The C_1-C_4 hydroxyalkyl group at R^7 is 1-hydroxyethyl, 1-hydroxypropyl, 1-hydroxybutyl or the like.

The optionally substituted saturated or unsaturated heterocyclic group at R^7 is a 5 or 6-membered aromatic heterocyclic group optionally containing 1 - 3 hetero atom(s) selected from nitrogen atom, oxygen atom and sulfur atom, such as a group derived from furan, thiophene, pyrrole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, imidazole, furazan, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, oxazoline, thiazoline, imidazoline and the like. These substituents include optionally substituted aryl group (phenyl or naphthyl optionally substituted by halogen, amino, nitro, hydroxyl group, C_1-C_4 alkyl, C_1-C_4 alkoxy and the like), C_1-C_{18} alkyl group (as defined above), C_1-C_2 halogenated alkyl group (as defined above), C_1-C_8 alkoxy group (as defined above), acyl (as defined above), and the like.

Examples of the optionally substituted fused aromatic heterocyclic group at R^7 include groups derived from benzofuran, benzothiophene, indole, benzoxazole, benzothiazole, 1,2-benzoisoxazole, 1,2-benzoisothiazole, benzimidazolyl and the like, with preference given to benzoxazol-2-yl and benzothiazol-2-yl. Examples of these substituents include halogen (fluorine, chlorine, bromine etc.), haloalkyl (fluoromethyl, difluoromethyl, trifluoromethyl etc.), C_1-C_4 alkyl (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.), C_1-C_8 alkoxy (methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy etc.), hydroxy, nitro, cyano, amino and the like.

X includes hydrogen atom, hydroxy, methoxy, ethoxy, isopropoxy and the like, with particular preference given to hydroxy.

Specific examples of R^1 include

1-benzylpiperidin-4-ylamino,

4-phenylcyclohexyl-1-ylamino,

indanon-2-ylamino,

4-hydroxy-4-(4-chlorophenyl)piperidino,

4-hydroxy-4-(2-naphthyl)piperidino,

4-hydroxy-4-(benzo(b)thiophen-2-yl)piperidin-1-yl,

4-benzylpiperidino,

4-(4-fluorobenzyl)piperidino,

4-(4-chlorobenzyl)piperidino,

4-(4-bromobenzyl)piperidino,

4-phenylpiperidino,

4-(4-fluorophenyl)piperidino,

4-(4-chlorophenyl)piperidino,

4-(4-bromophenyl)piperidino,

4-(4-methoxyphenyl)piperidino,

4-(4-methylphenyl)piperidino,

4-(4-trifluoromethylphenyl)piperidino,

4-(3-chlorophenyl)piperidino,

4-(3-fluorophenyl)piperidino,

4-(3-trifluoromethylphenyl)piperidino,

4-(3-bromophenyl)piperidino,

4-(3-methoxyphenyl)piperidino,

4-(3-methylphenyl)piperidino,

4-(2-fluorophenyl)piperidino,

4-(2-chlorophenyl)piperidino,

4-(2-bromophenyl)piperidino,

4-(2-methylphenyl)piperidino,

4-(2-methoxyphenyl)piperidino,

4-(3,4-dichlorophenyl)piperidino,

4-(3,4-dimethylphenyl)piperidino,

4-(3,4-dimethoxyphenyl)piperidino,

4-(3,4-methylenedioxyphenyl)piperidino,

4-(2,3-dimethoxyphenyl)piperidino,

4-(2,3-dimethylphenyl)piperidino,

4-(2,3-dichlorophenyl)piperidino,

4-(3,5-dimethoxyphenyl)piperidino,

4-(3,5-dimethylphenyl)piperidino,

4-(3,5-dichlorophenyl)piperidino,

4-(2,6-dimethoxyphenyl)piperidino,

4-(3,4,5-trimethoxyphenyl)piperidino,

4-(naphthalen-1-yl)piperidino,

4-(naphthalen-2-yl)piperidino,

4-(6-methoxynaphthalen-2-yl)piperidino,

4-(benzo(b)thiophen-2-yl)piperidino,

4-(benzo(b)furan-2-yl)piperidino,

4-(indol-2-yl)piperidino,

4-(4-fluorobenzyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(4-chlorobenzyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(4-bromobenzyl)-3,6-dihydro-2H-pyridin-1-yl,

4-phenyl-3,6-dihydro-2H-pyridin-1-yl,

4-(4-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(4-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(4-bromophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(4-methylphenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(4-trifluoromethylphenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(3-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(3-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(3-bromophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(3-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(3-methylphenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(2-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(2-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(2-bromophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(2-methylphenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(2-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,

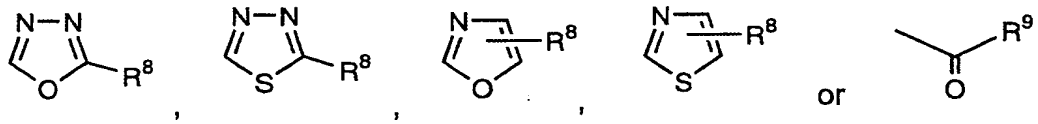
4-(3,4-dichlorophenyl)-3,6-dihydro-2H-pyridin-1-yl,

4-(3,4-dimethylphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(3,4-dimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(3,4-methylenedioxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(2,3-dimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(2,3-dimethylphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(2,3-dichlorophenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(3,5-dimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(3,5-dimethylphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(3,5-dichlorophenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(2,6-dimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(3,4,5-trimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl,
4-(naphthalen-1-yl)-3,6-dihydro-2H-pyridin-1-yl,
4-(naphthalen-2-yl)-3,6-dihydro-2H-pyridin-1-yl,
4-(6-methoxynaphthalen-2-yl)-3,6-dihydro-2H-pyridin-1-yl,
4-(benzo(b)thiophen-2-yl)-3,6-dihydro-2H-pyridin-1-yl,
4-(benzo(b)furan-2-yl)-3,6-dihydro-2H-pyridin-1-yl, and
and the like 4-(indol-2-yl)-3,6-dihydro-2H-pyridin-1-yl,

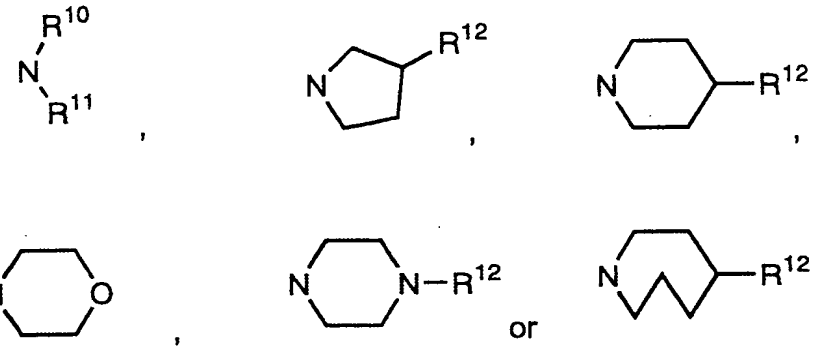
As R^1, particularly preferred are
4-(naphthalen-1-yl)piperidino,
4-(naphthalen-2-yl)piperidino,
4-(naphthalen-1-yl)-3,6-dihydro-2H-pyridin-1-yl,
4-(naphthalen-2-yl)-3,6-dihydro-2H-pyridin-1-yl,
and the like.

As R^3, hydrogen atom and C_1-C_4 alkyl (methyl, ethyl, propyl, isopropyl, butyl etc.) are preferable and hydrogen atom is particularly preferable.

As R^7, a group of the following formula is preferable:

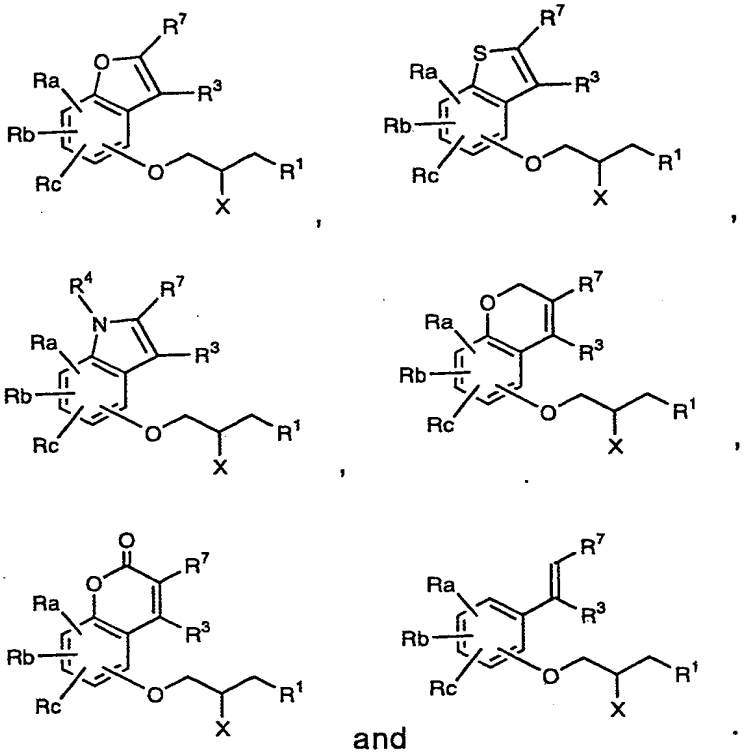


wherein
R^9 is a group of the following formula



As Ra, Rb and Rc, 0 to 3 may present on a ring. Ra, Rb and Rc includes hydrogen atom, fluorine, chlorine, bromine, methyl, ethyl, methoxy, methylenedioxy, hydroxy, acetyl and the like.

Preferable embodiment of the formula (I) includes the compounds of the following formulas:



The pharmaceutically acceptable salts of compounds of the formula (I) include acid addition salts with inorganic

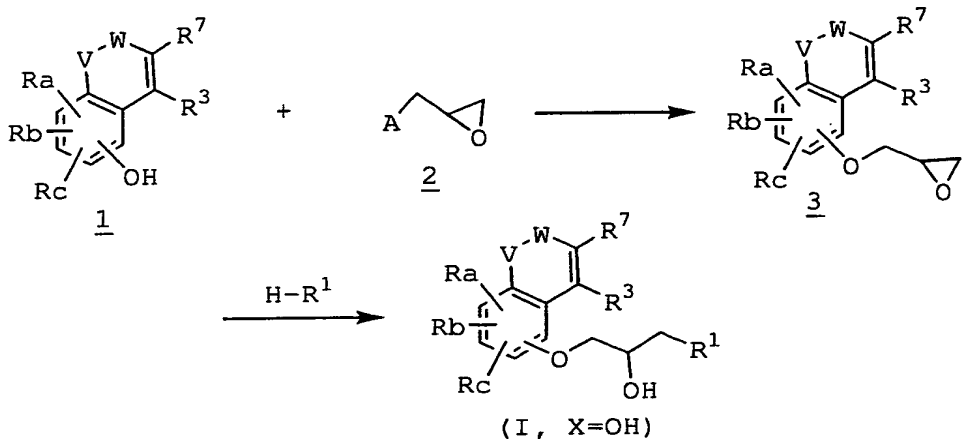
acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid etc.) or organic acids (e.g., acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, maleic acid, fumaric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, ascorbic acid, etc.).

The compounds of the formula (I) and pharmaceutically acceptable salts thereof may be present in the form of a hydrate or a solvate. These hydrates and solvates are also encompassed in the present invention. When the compound of the formula (I) has an asymmetric atom, at least two kinds of optical isomers exist. The optical isomers and racemates thereof are encompassed in the present invention.

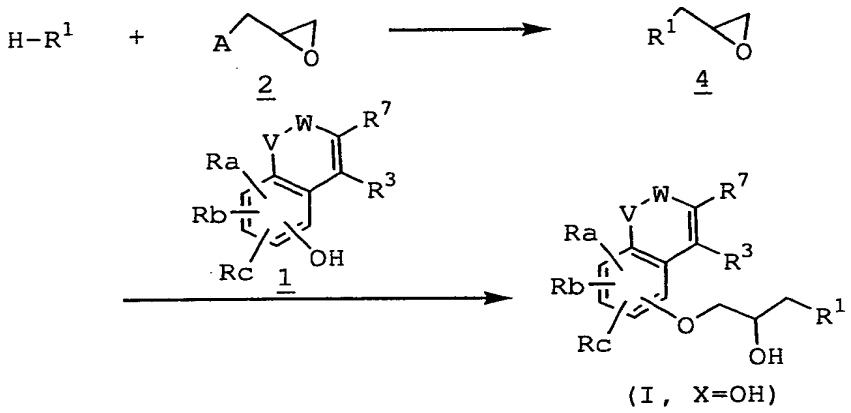
The compound of the formula (I), the inventive compounds encompassed in the formula (I), and the intermediate compounds can be synthesized by the following methods. Each symbol in the following reaction formulas is as defined above, unless particularly specified.

Many general synthesis methods for the compound of the formula (I) are known. The representative reaction schemes are shown in the following. In the formulas, the symbol A refers to a leaving group (or nucleofugal group) well known in the organic synthesis, such as chlorine, bromine, iodine, mesylate, tosylate, nosylate, triflate and the like.

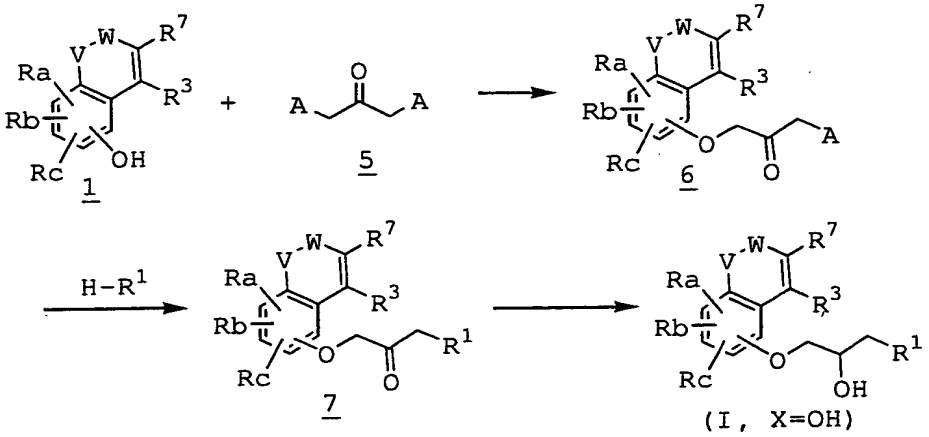
A


V
W
R7
Ra
R3
Rb
OH
Rc
1
+
A
O
2
3
H-R1
R1
(I, X=OH)

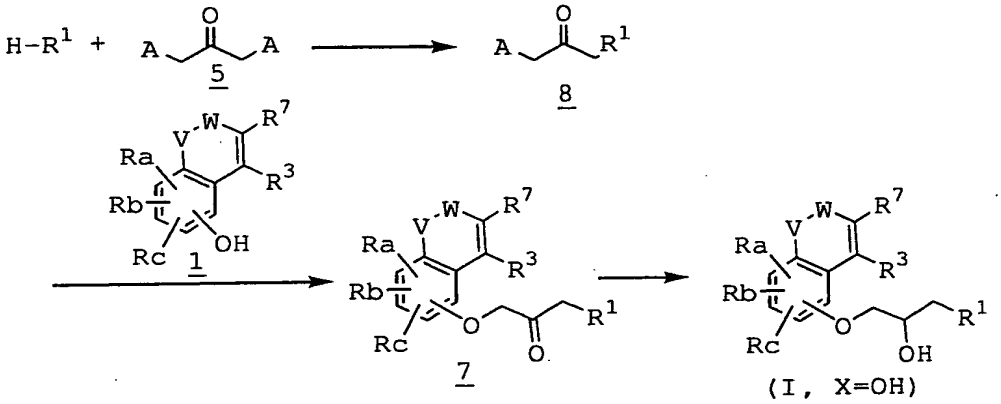
B


H-R1
+
A
O
2
R1
4
V
W
R7
Ra
R3
Rb
OH
Rc
1
(I, X=OH)

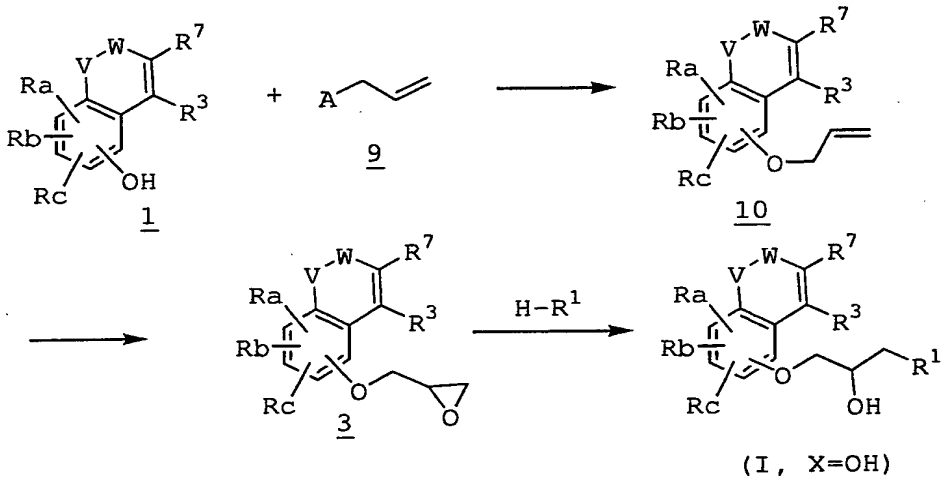
C



D



E



A method comprising reacting a phenol derivative (1) and 2,3-epoxypropane compound (2) having a leaving group at 1-

position, followed by reaction with H-R^1 (Reaction formula A), a method comprising reacting H-R^1 and 2,3-epoxypropane (2) having a leaving group at 1-position followed by reaction with a phenol derivative (1) (Reaction formula B),

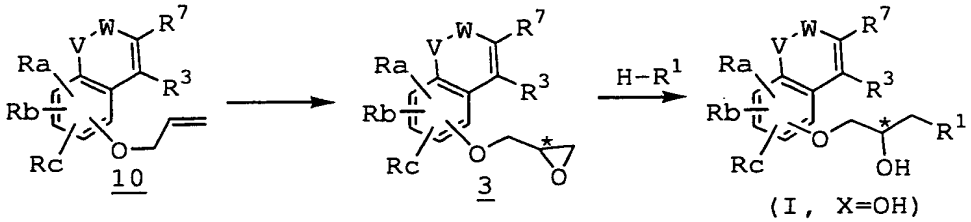
a method comprising reacting a phenol derivative (1) and 2-propanone (5) having leaving groups at 1,3-positions followed by reaction with H-R^1 to give a product (7), followed by reduction thereof (Reaction formula C),

a method comprising reacting H-R^1 and 2-propanone (5) having leaving groups at 1,3-position followed by being reacted with phenol derivative (1) to give a product (7), followed by reduction thereof (Reaction formula D),

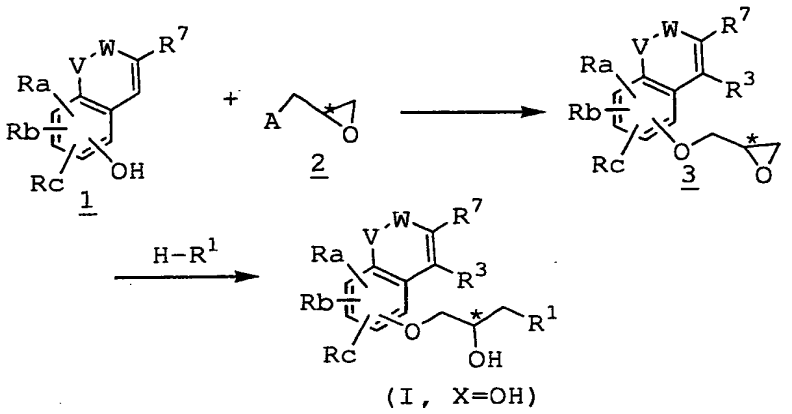
a method comprising reacting phenol derivative (1) and allyl compound (9) (e.g., 3-allyl bromide etc.) having a leaving group at 3-position to give a product (10), which is epoxidated and successively reacted with H-R^1 (Reaction formula E), and the like are exemplified. The methods for synthesis of the compound of the formula (I) are not limited to those mentioned above.

Particularly, the optically active compound of the formula (I) (X=OH) can be synthesized by the following Reaction formulas F, G, H, I, J, K, L and the like.

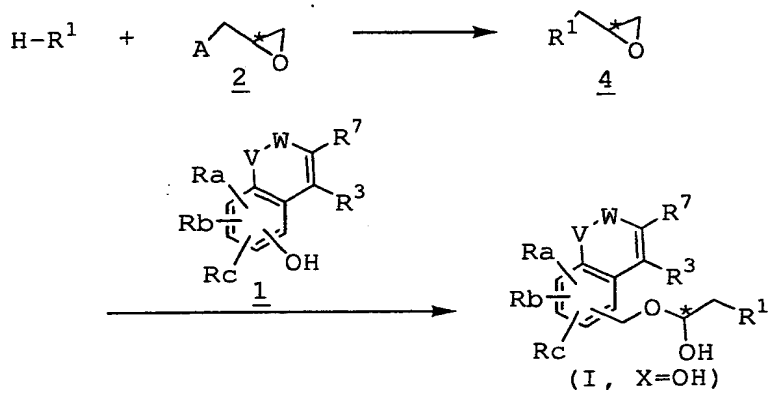
F


Ra
Rb
Rc
V
W
R7
R3
O
10
3
H-R1
R1
OH
(I, X=OH)

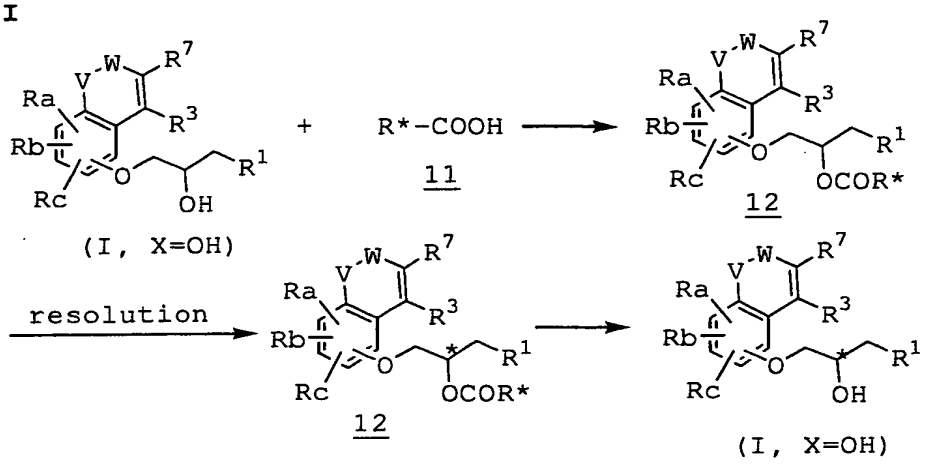
G


Ra
Rb
Rc
V
W
R7
R3
OH
1
A
2
3
H-R1
R1
(I, X=OH)

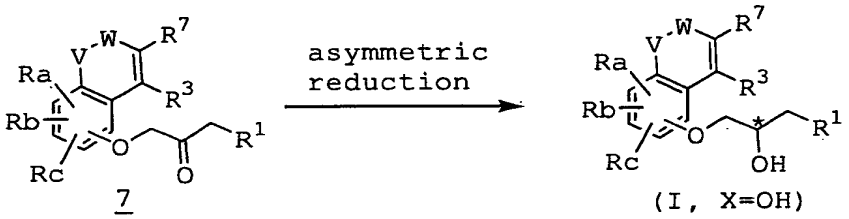
H


H-R1
A
2
R1
4
Ra
Rb
Rc
V
W
R7
R3
OH
1
R1
(I, X=OH)

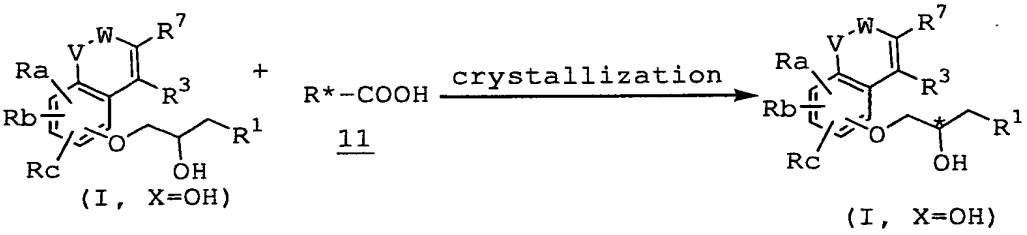
I



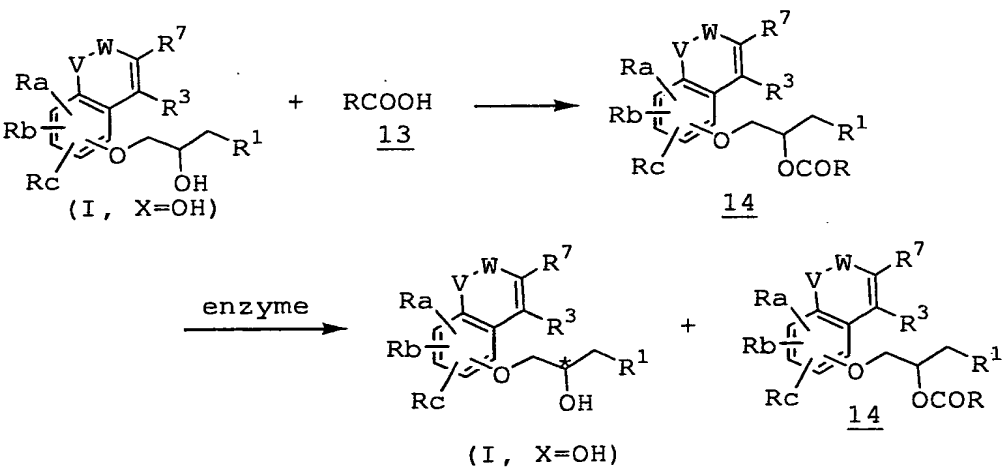
J



K



L



In these Reaction formulas, the symbol R* means a part other than carboxy group of optically active carboxylic acid. A method comprising asymmetric epoxydation of intermediate (10)

obtained by the above-mentioned Reaction formula E, using optically active base and asymmetric ligand in catalytic or stoichiometric amounts to give optically active intermediate (3), which is reacted with $H-R^1$ (Reaction formula F),

a method comprising reacting phenol derivative (1) and optically active 2,3-epoxypropane derivative (2) having a leaving group at 1-position followed by reaction with $H-R^1$ (Reaction formula G),

a method comprising reacting $H-R^1$ and optically active 2,3-epoxypropane derivative (2) having a leaving group at 1-position followed by reaction with phenol derivative (1) (Reaction formula H),

a method comprising condensing a racemic mixture of the compound of the formula (I) with optically active carboxylic acid (11) to convert the compound to optically active ester (12), which is followed by crystallization, column chromatography and the like to resolve the compound into two diastereomers (Reaction formula I),

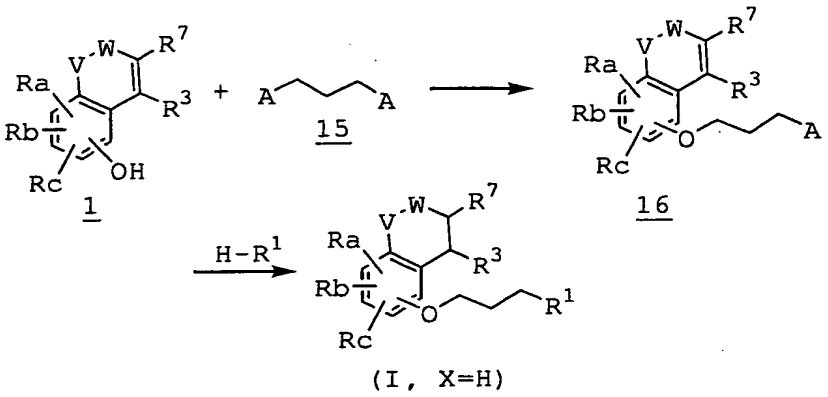
a method comprising asymmetric reduction of intermediate (7) obtained by the above-mentioned Reaction formulas C and D, using a chiral ligand (Reaction formula J),

a method comprising forming a salt in a racemic mixture of the compound of the formula (I) and optically active carboxylic acid (11), whereby both isomers are resolved based on difference in crystallinity (Reaction formula K),

a method comprising condensing a racemic mixture of the compound of the formula (I) with carboxylic acid to once convert the compound to an ester, and hydrolyzing the ester enantioselectively using an enzyme (Reaction formula L), and the like are exemplified.

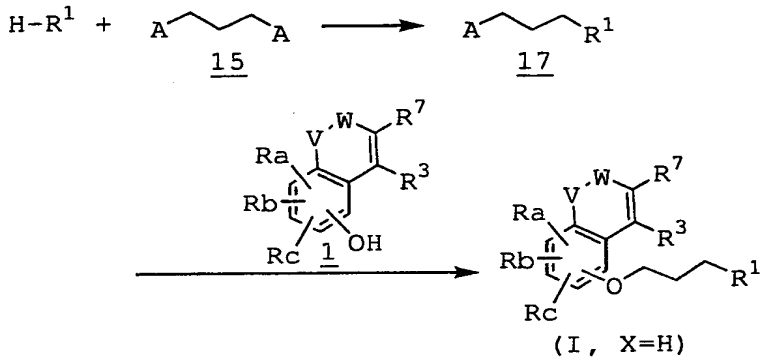
A compound of the formula (I) wherein X is hydrogen atom can be synthesized as in the following Reaction formulas M and N and the like.

M



(I, X=H)

N



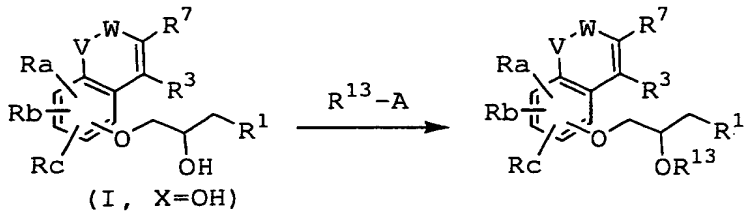
(I, X=H)

A method comprising reacting phenol derivative (1) and propane derivative (15) having leaving groups or nucleofugal groups at 1,3-positions to synthesize intermediate (16), and condensing the intermediate (16) and $H-R^1$ in the presence of deoxidizing agent (Reaction formula M),

a method comprising reacting $H-R^1$ and propane derivative (15) having leaving groups or nucleofugal groups at 1,3-positions to synthesize intermediate (17) and condensing the intermediate (17) and phenol derivative (1) in the presence of deoxidizing agent (Reaction formula N), and the like are exemplified.

Of the compounds of the formula (I), a compound wherein X is alkoxy can be derived from the compound of the formula (I) wherein X is OH as in the following Reaction formula O.

O



(I, X=OH)

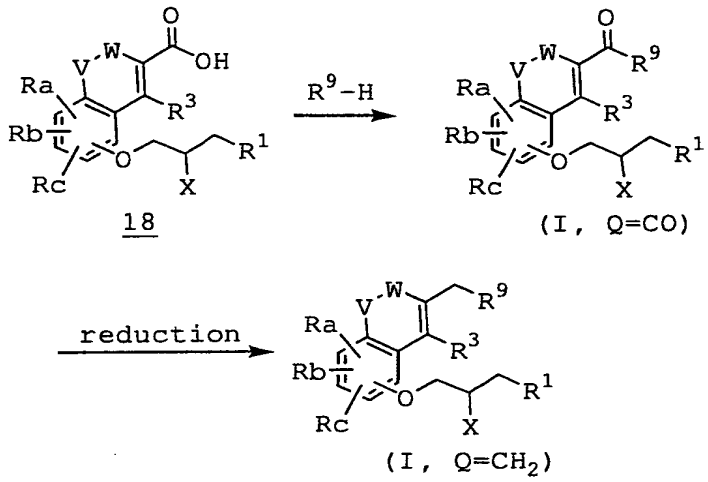
(I,X=alkyl)

The symbol R^{13} represents alkyl group.

The compound wherein X is alkoxy group can be synthesized by alkylating hydroxy group of a compound of the formula (I) wherein X is OH, in the presence of deoxidizing agent (Reaction formula O).

Of the compounds of the formula (I), a compound wherein R^7 is the formula: $-Q-R^9$ wherein Q is CO or CH_2 can be derived from carboxylic acid derivative (18), as in the following Reaction formula P.

P



18

(I, Q=CO)

(I, $Q=CH_2$)

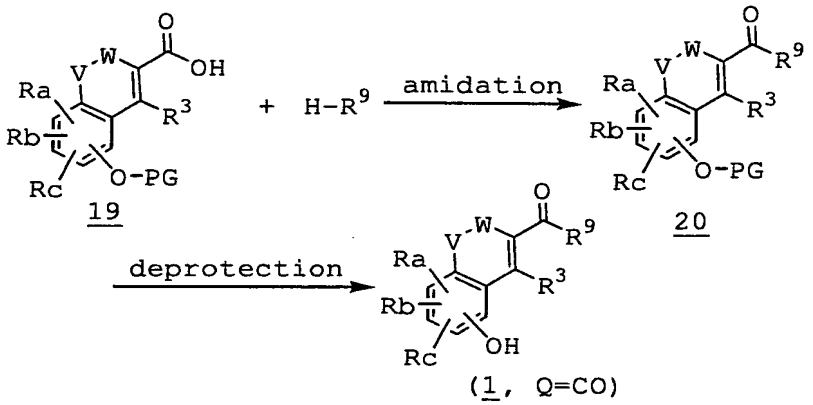
Amide compound (Q=CO) can be synthesized by condensing carboxylic acid derivative (18) with $H-R^9$ in the presence of amidating agent (Reaction formula P). Amino compound ($Q=CH_2$) can be synthesized by reducing the amide compound. The amidating agent to be used is exemplified by dicyclohexylcarbodiimide (DCC), diethyl cyanophosphate, diphenylphosphoryl azide (DPPA), 1,1'-carbonylbis-1H-imidazole (CDI), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (WSC) and the like. The reducing agent to be used is exemplified by lithium aluminum hydride, diisopropyl aluminum hydride, diborane, sodium borohydride and the like.

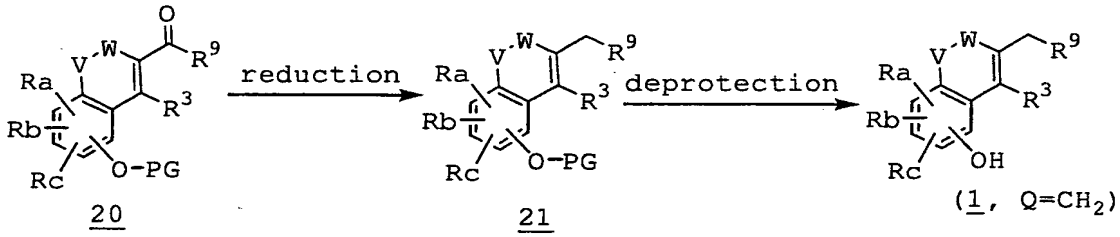
Of the phenol derivatives (1) used in Reaction formulas A, B, D, E, G, H, M and N, a compound wherein R^7 is the formula:

$-Q-R^9$ can be synthesized according to the following reaction formulas Q, R, S and the like. In these reaction formulas, the symbol PG means hydrogen atom or a protecting group (e.g., methyl, ethyl, methoxymethyl, ethoxymethyl, trimethylsilyl, benzyl, acetyl, benzoyl etc.) that can be eliminated easily in the organic synthesis.

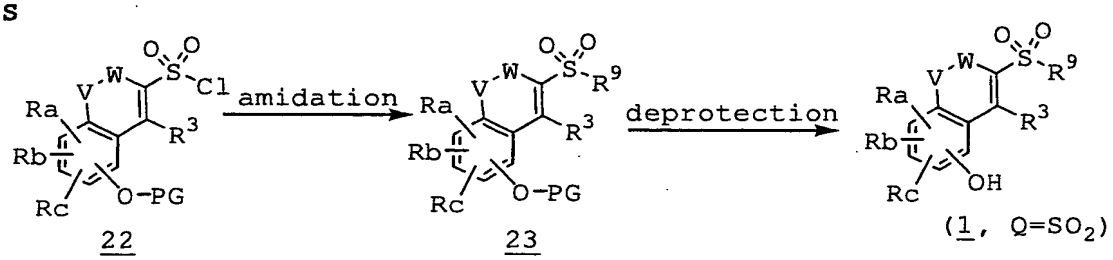
Q



R



S



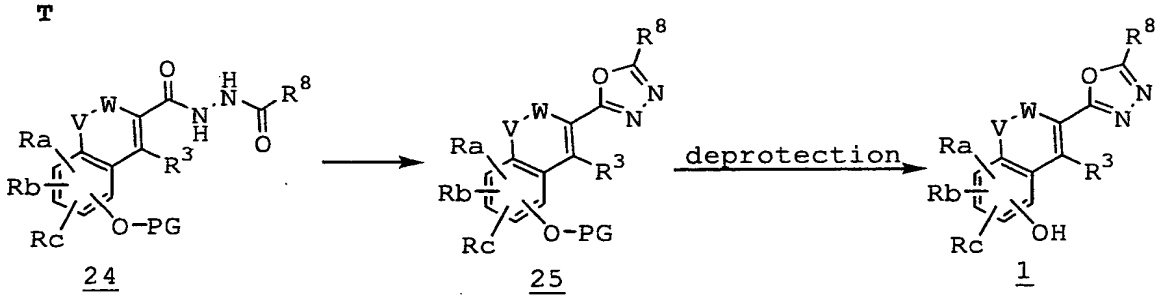
Phenol derivatives (1, Q=CO) can be synthesized by condensing carboxylic acid derivative (19) with R^9, using amidating agent (Reaction formula Q), and then eliminating the protecting group. As the amidating agent, dicyclohexylcarbodiimide (DCC), diethyl cyanophosphate, diphenylphosphoryl azide (DPPA), 1,1'-carbonylbis-1H-imidazole (CDI), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) and the like can be used.

Phenol derivative (1, $Q=CH_2$) can be synthesized by reducing amide compound (20) with a reducing agent (Reaction formula R), and eliminating the protecting group. As the reducing agent, lithium aluminum hydride, diisopropyl aluminum hydride, diborane, sodium borohydride and the like can be used.

Phenol derivative (1, $Q=SO_2$) can be synthesized by condensing, sulfonic chloride derivative (22) with $H-R^9$ using a deoxidizing agent (Reaction formula S), and eliminating the protecting group.

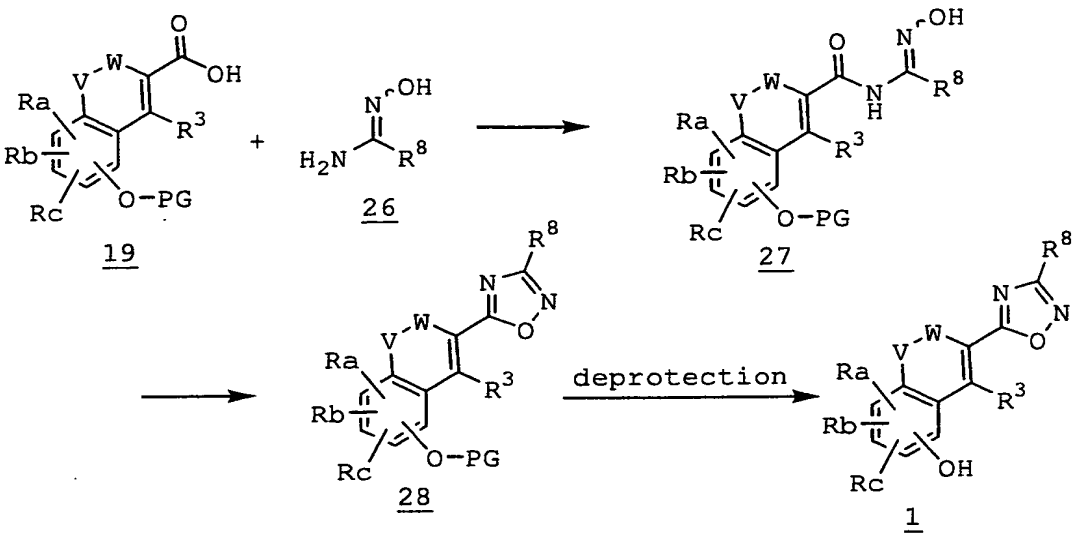
In the following, the reaction formulas T, U, V, W, X, Y, and Z are shown as general synthetic methods of representative compounds wherein R^7 is optionally substituted heterocycle among phenol derivatives (I) used in the reaction formulas A, B, D, E, F, G, H, I, J, K, L, M, N and O.

T



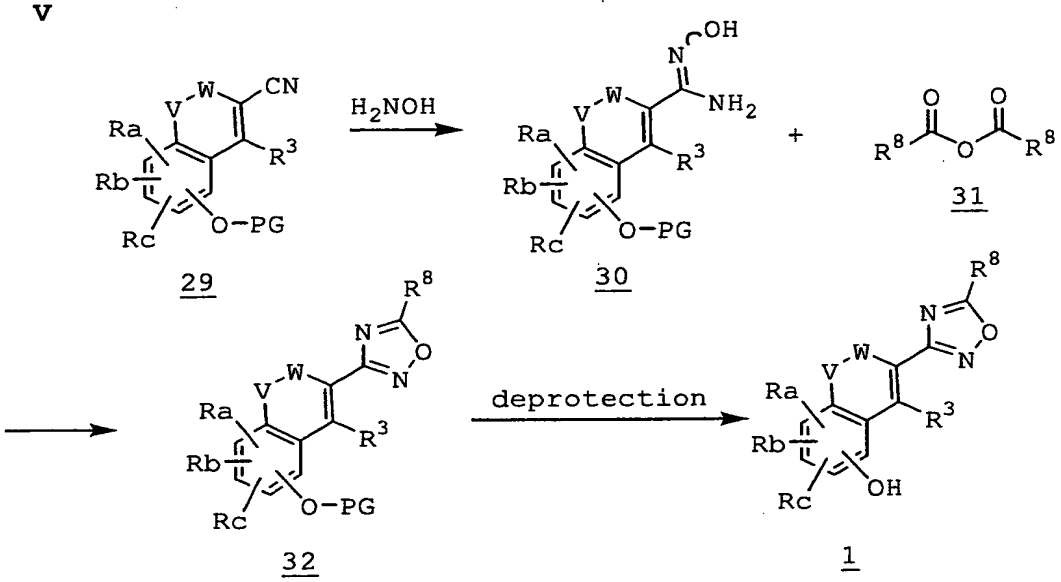
24 25 1

U



19 26 27 28 1

V



29 30 31 32 1

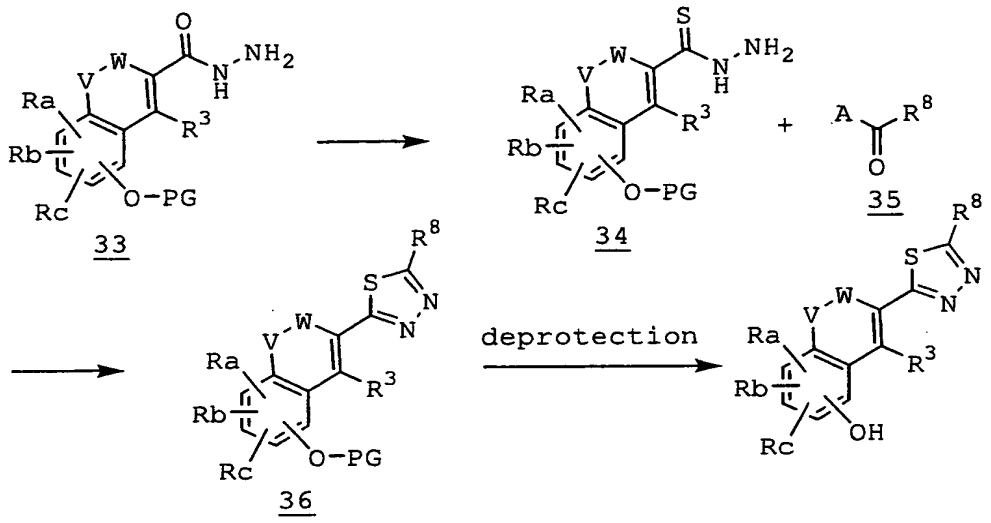
The 1,3,4-oxadiazole derivatices such as of the Reaction formula T can synthesized by cyclization of diacylhydrazine derivative (24) with a dehydrating agent or reacting azo compound and triphenylphosphine, in the presence of a deoxidizing agent, followed by deprotection. As the dehydrating agent, polyphosphoric acid, phosphorus pentachloride, phosphorus trichloride, sulfuric acid, phosphorus oxychloride, thionyl chloride, oxalyl chloride and the like can be used. As the azo compound, diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD)

and the like can be used.

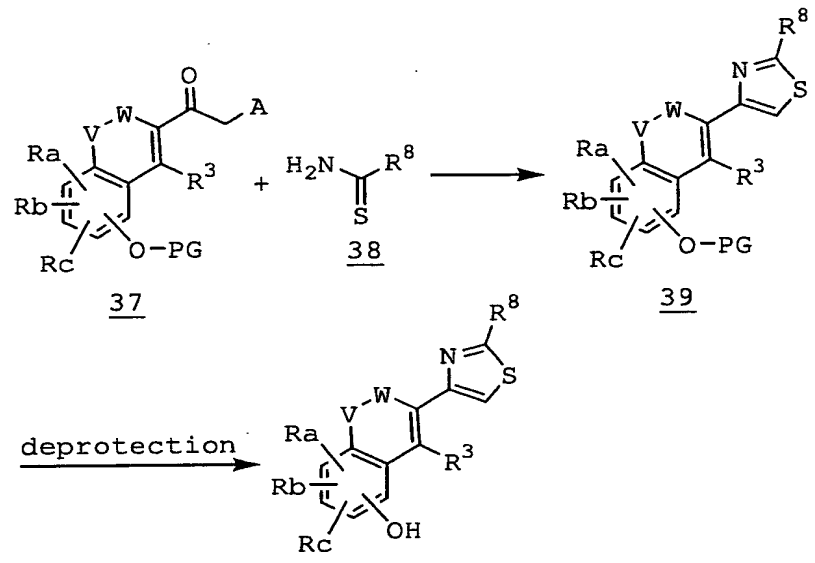
The 1,2,4-oxadiazole derivatives such as of the Reaction formula U can be synthesized by condensing carboxylic acid derivative (19) and hydroxyimino compound 26 using an amidating agent to give compound (27), which is subjected to cyclization using a dehydrating agent or by heating for dehydration, followed by deprotection. As the dehydrating agent, polyphosphoric acid, phosphorus pentachloride, phosphorus trichloride, sulfuric acid, phosphorus oxychloride, thionyl chloride, oxalyl chloride and the like can be used.

The 1,2,4-oxadiazole derivatives such as of the Reaction formula V can be synthesized condensing nitrile derivative (29) and hydroxylamine to give compound (30), to which acid anhydride (31) is added to allow cyclization by heating for dehydration, followed by deprotection.

W

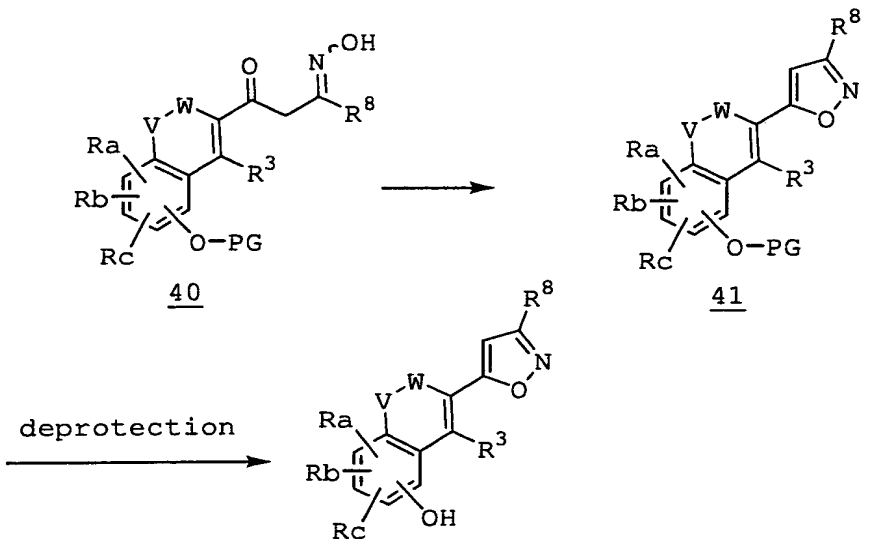


X

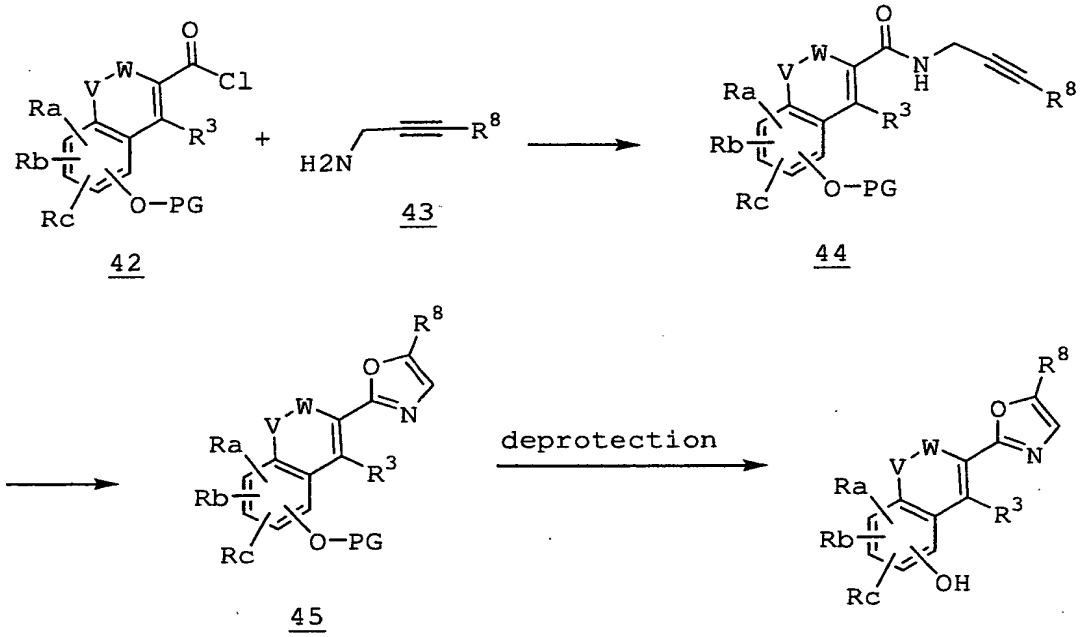


The 1,3,4-thiadiazole derivatives such as of the Reaction formula W can be synthesized by conversion of hydrazone compound (33) into thione compound with a sulfidation agent to give compound (34), which is cyclized with compound (35) by heating, followed by deprotection. As the sulfidation agent, Lawesson reagent, diphosphorus pentasulfide and the like can be used. Thiazole derivatives such as of the Reaction formula X can be synthesized by cyclization of compound (37) and thioamide compound (38) by heating, followed by deprotection.

Y



Z



The isoxazole derivatives such as of the Reaction formula Y can be synthesized by cyclization of hydroxyimino compound (40), using a dehydrating agent or by heating for dehydration, followed by deprotection. As the dehydrating agent, polyphosphoric acid, phosphorus pentachloride,

phosphorus trichloride, sulfuric acid, phosphorus oxychloride, thionyl chloride, oxalyl chloride and the like can be used. Oxazole derivatives such as reaction formula Z can be synthesizede by condensing acid halide compound (42) and acetylene compound (43) to give compound (44), followed by cyclization under heating using mercury(II) acetate and deprotection.

The compounds of the formula (I) obtained as mentioned above have high affinity for 5-HT_{1A} receptors and have a 5-HT reuptake inhibitory action. Therefore, the compounds can provide effective pharmaceutical agents for diseases accompanying serotoninergic neurotransmission functional disorders.

That is, the inventive compounds show quick expression of the anti-depressive effect and are useful as a so-called rapid onset antidepressant. They are also useful for the treatment of mammals inclusive of human for central nervous system diseases mediated by 5-HT, such as schizophrenia, anxiety neurosis, obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, seasonal emotional disorder, Anorexia Nervosa, Bulimia Nervosa, nocturnal enuresis, children's hyperlocomotion, post-traumatic stress disorder (PTSD), senile dementia, hemicrania, stroke, Alzheimer's disease, recognition disorder, hypertension, gastrointestinal injury, feeding disorders, abnormal body temperature regulation and sexual disorder, pain, as well as abnormal cardiovascular system, drug abuse and the like.

When the compound of the present invention is used as a pharmaceutical agent, a systemic administration of a pharmacologically acceptable amount of the compound of the formula (I) or a pharmacologically acceptable acid addition salt thereof to a mammal is included. The dose requires careful control for each case, and in consideration of age,

weight and the condition of the subject, administration route, as well as nature and severity of disease, the general daily dose in the case of parenteral administration is 0.01 - 100 mg/kg, preferably 0.1 - 1 mg/kg, and that in the case of oral administration is 0.5 - 10 mg/kg, preferably 1 - 5 mg/kg. Administration includes oral, rectal and parenteral (e.g., intramuscular, intravenous, percutaneous and subcutaneous) administrations.

For anti-depression, the compound of the present invention may be administered as a single therapeutic agent or may be administered as a mixture with other therapeutic agents. For therapy, the compound is generally given as a pharmacological composition containing the compound of the formula (I) or a pharmaceutically acceptable salt thereof in an amount sufficient to show an anti-depressive effect, and a pharmaceutically acceptable carrier. A pharmacological composition containing about 1 - 500 mg of the active ingredient per unit dose is desirable. According to a conventional method, it is prepared into tablets, lozenges, capsules, powders, aqueous or oily suspensions, syrups, elixirs, aqueous solutions and the like. The pharmacological composition to be used naturally shows properties that vary depending on the objective administration route. For example, an oral composition may be tablet or capsule, and may contain a conventional excipient such as binder (starch etc.) and moistening agent (sodium laurylsulfate etc.). A solution or suspension of the present invention containing a conventional pharmacological vehicle may be used for parenteral administration, such as an aqueous solution for intravenous injection and oily suspension for intramuscular injection.

【Examples】

The present invention is described in detail in the following by Starting Material Synthesis Examples, Examples, Formulation Examples and Experimental Examples. The present

invention is not limited in any way by these examples.

Starting Material Synthesis Example 1

(S)-1-(4-glycidyloxybenzo(b)furan-2-ylcarbonyl)pyrrolidine

To a solution (30 ml) of (S)-1-(4-hydroxybenzo(b)furan-2-ylcarbonyl)pyrrolidine (1.3 g) in DMF were added potassium carbonate (2.2 g) and (S)-glycidyl nosylate (1.7 g), and the mixture was stirred at room temperature for 10 hr, followed by pouring into water. After extraction with ethyl acetate, the oil layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (1.2 g) as a yellow oil.

^{1}H-NMR($CDCl_3$)δ:1.93(penth, J=6.4, 2H),.2.00(penth, J=6.4, 2H), 2.79(dd, J=4.9, 2.9, 1H), 2.93(t, J=4.9, 1H), 3.38-3.43(m, 1H), 3.69(t, J=6.8, 2H), 3.92(t, J=6.8, 2H), 4.08(dd, J=11.2, 5.8, 1H), 4.36(dd, J=11.2, 3.0, 1H), 6.00(d, J=8.3, 1H), 7.15(d, J=8.3, 1H), 7.28(t, J=8.3, 1H), 7.47(s, 1H)

Starting Material Synthesis Example 2

(S)-4-(4-glycidyloxybenzo(b)furan-2-ylcarbonyl)morpholine

To a suspension (30 ml) of sodium hydride (0.52 g) in DMF was dropwise added a solution (30 ml) of 4-(4-hydroxybenzo(b)furan-2-yl)morpholine in DMF at a reaction temperature of 4°C over 10 min, and the mixture was stirred for 30 min. Thereto was added a solution (10 ml) of (S)-glycidyl nosylate (3.4 g) in DMF, and the mixture was stirred for 30 min and poured into water. After extraction with ethyl acetate, the oil layer was washed with water, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (1.3 g) as a yellow oil.

^{1}H-NMR($CDCl_3$)δ:2.81(dd, J=4.9, 2.4, 1H), 2.96(t, J=4.9, 1H), 3.42-3.44(m, 1H), 3.78-4.07(m, 8H), 4.09(dd, J=10.8, 5.9, 1H), 4.40(dd, J=10.8, 3.0, 1H), 6.69(d, J=8.3, 1H), 7.16(d,

J=8.3,1H), 7.32(t, J=8.3, 1H), 7.44(s, 1H)

Starting Material Synthesis Example 3

Methyl (S)-4-glycidyloxybenzo(b)furan-2-carboxylate

To a solution (60 ml) of methyl 4-hydroxybenzo(b)furan-2-carboxylate (3.6 g) in N,N-dimethylformamide (DMF) were added (S)-glycidyl nosylate (5.1 g) and potassium carbonate (6.5 g) and the mixture was stirred at room temperature for 8 hr. The reaction mixture was evaporated under reduced pressure and ethyl acetate was added to the residue. The mixture was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (4.1 g) as a yellow crystalline compound.

^{1}H-NMR($CDCl_3$)δ:2.82(dd, J=4.9, 3.0, 1H), 2.96(t, J=4.9, 1H), 3.41-3.45(m, 1H), 3.97(s, 3H), 4.09(dd, J=10.8, 5.9, 1H), 4.40(dd, J=10.8, 3.0, 1H), 6.69(d, J=8.3, 1H), 7.22(d, J=8.3,1H), 7.36(t, J=8.3, 1H), 7.68(s, 1H)

Starting Material Synthesis Example 4

4-(8-methoxy-2H-chromen-3-ylcarbonyl)morpholine

To a solution (200 ml) of 8-methoxy-2H-chromene-3-carboxylic acid (10.0 g) in DMF were added triethylamine (8.6 ml) and diethyl cyanophosphate (10.0 ml) and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The oil layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was concentrated under reduced pressure and the residue was purified by silica gel chromatography (chloroform/ethyl acetate) to give the title compound (3.5 g) as a brown oil.

^{1}H-NMR($CDCl_3$)δ:3.69-3.78(m, 8H), 4.94(s, 2H), 6.60(s, 1H), 6.71(d, J=5.2, 1H), 6.87-6.90(m, 2H)

Starting Material Synthesis Example 5

4-(8-hydroxy-2H-chromen-3-ylcarbonyl)morpholine

To a solution (70 ml) of 4-(8-methoxy-2H-chromen-3-ylcarbonyl)morpholine (3.5 g) in methylene chloride was added

dropwise boron tribromide (9.5 g) at -78°C. The reaction temperature was set to room temperature and the mixture was stirred for 2 hr. The reaction mixture was poured into water and stirred for 1 hr. The oil layer was separated and washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (3.3 g) as brown crystals.

^{1}H-NMR($CDCl_3$)δ:3.69-3.73(brs, 8H), 4.95(s, 2H), 5.83(brs, 1H), 6.61(s, 1H), 6.65(d, J=7.3, 1H), 6.83(t, J=7.3, 1H), 7.89(d, J=7.3, 1H)

Starting Material Synthesis Example 6

(S)-4-(8-glycidyloxy-2H-chromen-3-ylcarbonyl)morpholine

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 4-(8-hydroxy-2H-chromen-3-ylcarbonyl)morpholine (3.3 g), potassium carbonate (3.5 g) and (S)-glycidyl nosylate (3.3 g), the title compound (3.1 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ:2.74(dd, J=4.9, 2.4, 1H), 2.91(t, J=4.9, 1H), 3.37-3.39(m, 1H), 3.69-3.73(brs, 8H), 4.03(dd, J=11.7, 5.8, 1H), 4.11-4.13(m, 1H), 4.28(dd, J=11.7, 3.4, 1H), 4.94(s, 2H), 6.60(s, 1H), 6.75(d, J=7.3, 1H), 6.87(t, J=7.3, 1H), 6.91(d, J=7.3, 1H)

Starting Material Synthesis Example 7

8-methoxy-N,N-dimethyl-2H-chromene-3-carboxamide

By the reactions in the same manner as in Starting Material Synthesis Example 4 using 8-methoxy-2H-chromene-3-carboxylic acid (8.0 g), triethylamine (14.0 ml) and diethyl cyanophosphate (8.2 ml), the title compound (3.2 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ:3.83(s, 6H), 4.84(s, 2H), 6.45(d, J=8.3, 1H), 6.50(d, J=8.3, 1H), 6.99(s, 1H), 7.13(t, J=8.3, 2H)

Starting Material Synthesis Example 8

(S)-8-glycidyloxy-N,N-dimethyl-2H-chromene-3-carboxamide

By the reactions in the same manner as in Starting

Material Synthesis Example 5 using 8-methoxy-N,N-dimethyl-2H-chromene-3-carboxamide (3.2 g) and boron tribromide (11.0 g), a brown oil (3.0 g) was obtained. To a solution (50 ml) of this brown oil in DMF were added potassium carbonate (3.8 g) and (S)-glycidyl nosylate (3.8 g), and the mixture was stirred at room temperature for 10 hr and poured into water. After extraction with ethyl acetate, the oil layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (3.2 g) as yellow crystals, melting point 115-117°C.

Starting Material Synthesis Example 9

Ethyl 4-benzyloxy-1-methyl-indole-2-carboxylate

To a solution (100 ml) of ethyl 4-benzyloxy-1H-indole-2-carboxylate (12.0 g) in DMF was added sodium hydride (1.6 g) and the mixture was stirred at room temperature for 10 min. To this reaction mixture was added methyl iodide (2.2 g) and the mixture was stirred for 1 more hr. The reaction mixture was poured into water and extracted with ethyl acetate. The oil layer was washed with saturated aqueous solution of ammonium chloride and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (13.2 g) as a brown oil.

^{1}H-NMR($CDCl_3$)δ:1.39(t, J=6.9, 3H), 4.06(s, 3H), 4.35(q, J=6.9, 2H), 5.22(s, 2H), 6.66(d, J=7.8, 1H), 6.98(t, J=7.8, 1H), 7.40(t, J=7.4, 1H), 7.45-7.51(m, 6H)

Starting Material Synthesis Example 10

Ethyl 4-hydroxy-1-methyl-indole-2-carboxylate

To a solution (200 ml) of ethyl 4-benzyloxy-1-methylindole-2-carboxylate (13.0 g) in ethanol was added 10% palladium-carbon (1.3 g), and the mixture was stirred at room temperature for 8 hr under a hydrogen atmosphere. The palladium-carbon was filtered off with celite and the reaction

mixture was concentrated under reduced pressure to give the title compound (8.0 g) as a brown oil.

^{1}H-NMR($CDCl_3$)δ:1.40(t, J=6.9, 3H), 4.05(s, 3H), 4.37(q, J=6.9, 2H), 6.52(d, J=7.8, 1H), 6.95(t, J=7.8, 1H), 7.19(t, J=7.4, 1H), 7.41(s, 1H)

Starting Material Synthesis Example 11

Ethyl 4-benzyloxy-1-(2-methylpropyl)-indole-2-carboxylate

By the reactions in the same manner as in Starting Material Synthesis Example 9 using ethyl 4-benzyloxy-indole-2-carboxylate (10.0 g), sodium hydride (1.6 g) and isobutyl iodide (3.3 ml), the title compound (6.0 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ:0.89(d, J=6.3, 6H), 1.39(t, J=7.3, 3H), 2.22(penth, J=6.3, 1H), 4.25-4.42(m, 2H), 4.35(q, J=7.3, 1H), 5.21(s, 2H), 6.54(d, J=7.8, 1H), 7.00(d, J=7.8, 1H), 7.20(t, J=7.8, 1H), 7.33-7.1(m, 5H)

Starting Material Synthesis Example 12

Ethyl 4-hydroxy-1-(2-methylpropyl)-indole-2-carboxylate

By the reactions in the same manner as in Starting Material Synthesis Example 10 using ethyl 4-benzyloxy-1-(1-methylethyl)-indole-2-carboxylate (6.0 g) and 10% palladium-carbon (0.6 g), the title compound was obtained as pale-brown crystals.

^{1}H-NMR($CDCl_3$)δ:0.89(d, J=6.3, 6H), 1.40(t, J=7.3, 3H), 2.21(penth, J=6.3, 1H), 4.25-4.42(m, 2H), 4.35(q, J=7.3, 1H), 6.49(d, J=7.8, 1H), 6.96(d, J=7.8, 1H), 7.16(t, J=7.8, 1H), 7.42(s, 1H)

Starting Material Synthesis Example 13

3-chloro-6-methoxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide

3.0 g of 3-chloro-6-methoxy-benzo(b)thiophene-2-carboxylic acid (7.0 g) synthesized from 4-methoxycinnamic acid (10.0 g) and thionyl chloride (15 ml) according to the method described in J. Med. Chem. 1992, 35, 958-965 was reacted with dimethylamine hydrochloride and triethylamine in THF to give

the title compound (1.9 g) as a brown oil.

^{1}H-NMR($CDCl_3$):3.09(bs, 3H), 3.12(bs, 3H), 3.89(s, 3H), 7.10(d, 1H, J=8.8), 7.26(s, 1H), 7.71(d, 1H, J=8.8)

Starting Material Synthesis Example 14

(S)-3-chloro-6-glycidyloxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide

3-Chloro-6-methoxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide (1.9 g) was dissolved in methylene chloride (100 ml) and the mixture was cooled to -78°C. Boron tribromide (4 ml) was added dropwise, and after the temperature rose to room temperature, the mixture was poured into water and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure to give the title compound (2.5g).

^{1}H-NMR($CDCl_3$):2.80(dd, 1H, J=4.8,2.9), 2.95(t, 1H, J=4.8), 3.11(bs, 3H), 3.17(bs, 3H), 3.41(m, 1H), 4.00(dd,1H, J=5.9,10.8), 4.35(dd,1H, J=3.0,11.5), 7.13(dd, 1H, J=2.5,8.7), 7.26(s, 1H), 7.72(d, 1H, J=8.8)

Starting Material Synthesis Example 15

4-methoxymethyloxybenzo(b)thiophene-2-carboxylic acid

4-Methoxymethyloxybenzo(b)thiophene (83 g) was dissolved in THF (700 ml) and the mixture was cooled to -78°C. At this temperature, a solution (363 ml) of n-butyllithium in hexane was added dropwise. The temperature was raised to 0°C and then cooled again to -35°C, and carbon dioxide was bubbled. After the completion of the reaction, the reaction mixture was poured into water, and in the presence of ice, hydrochloric acid was added to adjust its pH to 1 and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure to give the title compound (80 g).

^{1}H-NMR($CDCl_3$):3.55(s, 3H), 5.37(s, 2H), 7.04(d, 1H, J=7.8),

7.41(t, 1H, J=7.8), 7.50(d, 1H, J=8.2), 8.36(s, 1H)

Starting Material Synthesis Example 16

N,N-dimethyl-4-methoxymethyloxybenzo(b)thiophene-2-carboxamide

4-Methoxymethyloxybenzo(b)thiophene-2-carboxylic acid (9.6 g) obtained in Starting Material Synthesis Example 15 was dissolved in dimethylformamide (75 ml). Triethylamine (17 ml) and dimethylamine hydrochloride (4.9 g) were added and the mixture was stirred. After 15 min, diethyl cyanophosphate (10 ml) was added, and the mixture was stirred at room temperature for 3 hr. Aqueous hydrochloric acid was added under cooling to make the reaction mixture acidic (pH 1), and then the mixture was stirred at 45°C for 5 hr. The reaction mixture was poured into water, extracted three times with ethyl acetate and the organic layer was dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. To the obtained residue was added 6N aqueous hydrochloric acid and the mixture was stirred with heating at 50°C for 1 hr. The reaction mixture was extracted with ethyl acetate and the oil layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (9.0 g).

^{1}H-NMR($CDCl_3$):3.17(bs, 3H), 3.28(bs, 3H), 6.76(d, 1H, J=7.8), 7.23(t, 1H, J=7.8), 7.36(d, 1H, J=7.8), 7.81(s, 1H)

Starting Material Synthesis Example 17

(S)-4-glycidyloxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide

To a solution of N,N-dimethyl-4-hydroxymethyloxybenzo-(b)thiophene-2-carboxamide (9.0 g) in DMF (100 ml) was added potassium carbonate (8.0 g), and (S)-glycidyl nosylate (8.0 g) was further added. The mixture was stirred at 60°C for 2 hr. The reaction mixture was concentrated under reduced pressure and water was added. The mixture was extracted with ethyl acetate and the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate to give the

title compound (7.5 g).

^{1}H-NMR($CDCl_3$):2.81(dd, 1H, J=2.4,4.9), 2.96(t, 1H, J=4.4), 3.00-3.21(bs, 6H), 3.44-3.48(m, 1H), 4.08(dd, 1H, J=5.8,11.2), 4.41(dd, 1H, J=2.4, 11.2), 6.76(d, 1H, J=7.8), 7.32(t, 1H, J=7.8), 7.45(d, 1H, J=8.3), 7.73(s, 1H)

Starting Material Synthesis Example 18

(S)-4-(4-glycidyloxybenzo(b)thiophen-2-ylcarbonyl)morpholine

By the reactions in the same manner as in Starting Material Synthesis Example 16 using 4-methoxymethyloxy-benzo(b)thiophene-2-carboxylic acid (3.5 g), morpholine (1.0 g) and diethyl cyanophosphate (3.1 g), 4-(4-glycidyloxybenzo(b)thiophen-2-carbonyl)morpholine (3.2 g) was obtained as a brown oil. By the reactions in the same manner as in Starting Material Synthesis Example 1 using the brown oil (2.0 g) and (S)-glycidyl nosylate (2.1 g), the title compound (2.0 g) was obtained as brown crystals.

^{1}H-NMR($CDCl_3$):2.81(dd, 1H, J=1.9,4.8), 2.97(t, 1H, J=4.8), 3.42-3.48(m, 1H), 3.86-3.95(bs, 8H), 4.05(dd, 1H, J=5.6,11.2), 4.43(dd, 1H, J=2.9, 11.4), 6.77(d, 1H, J=8.3), 7.33(t, 1H, J=7.8), 7.45(d, 1H, J=7.8), 7.68(s, 1H)

Starting Material Synthesis Example 19

(S)-1-(4-glycidyloxybenzo(b)thiophen-2-ylcarbonyl)pyrrolidine

By the reactions in the same manner as in Starting Material Synthesis Example 16 using 4-methoxymethyloxybenzo(b)thiophene-2-carboxylic acid (3.0 g), pyrrolidine (0.75 g) and diethyl cyanophosphate (2.5 g), 1-(4-glycidyloxybenzo(b)thiophen-2-carbonyl)pyrrolidine (2.4 g) was obtained as a brown oil. By the reactions in the same manner as in Starting Material Synthesis Example 1 using the brown oil (2.0 g) and (S)-glycidyl nosylate (2.0 g), the title compound (0.45 g) was obtained as brown crystals.

^{1}H-NMR($CDCl_3$):1.98-2.10(bs, 4H), 2.80(dd, 1H, J=2.9, 4.9), 2.96(t, 1H, J=4.2), 3.42-3.48(m, 1H), 3.70(bs, 2H), 3.87(bs, 2H), 4.07(dd, 1H, J=4.8,11.2), 4.41(dd, 1H, J=2.9, 11.2), 6.74(d, 1H, J=7.8), 7.32(t, 1H, J=7.8), 7.44(d, 1H, J=8.3), 8.00(s, 1H)

Starting Material Synthesis Example 20

(S)-4-glycidyloxy-N-methoxy-N-methylbenzo(b)thiophene-2-carboxamide

By the reactions in the same manner as in Starting Material Synthesis Example 16 using 4-methoxymethyloxybenzo(b)thiophene-2-carboxylic acid (4.5 g), N,O-dimethylhydroxylamine hydrochloride (2.1 g) and diethyl cyanophosphate (3.2 g), 4-hydroxybenzo(b)thiophene-N-methoxy-N-methyl-2-carboxamide (4.0 g) was obtained as a brown oil. By the reactions in the same manner as in Starting Material Synthesis Example 1 using the brown oil (2.0 g) and (S)-glycidyl nosylate (2.0 g), the title compound (1.1 g) was obtained as brown crystals.

^{1}H-NMR($CDCl_3$):2.78(dd, 1H, J=2.8, 4.8), 2.98(t, 1H, J=4.2), 3.42(s, 3H), 3.43-3.48(m, 1H), 3.83(s, 3H), 4.10(dd, 1H, J=4.9,11.2), 4.36(dd, 1H, J=3.5, 11.3), 6.74(d, 1H, J=7.8), 7.33(t, 1H, J=8.3), 7.44(d, 1H, J=8.3), 8.40(s, 1H)

Starting Material Synthesis Example 21

methyl (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-carboxylate

To a solution (70 ml) of methyl (S)-4-glycidyloxybenzo(b)furan-2-carboxylate (4.1 g) obtained in Starting Material Synthesis Example 3 in methanol (70 ml) was added 4-(naphthalen-2-yl)piperidine (3.5 g) at room temperature, and the mixture was refluxed under heating for 2 hr. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (chloroform:methanol) to give the title compound (5.6 g) as yellow crystals, melting point 118-119°C.

Starting Material Synthesis Example 22

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-carboxylic acid

To a solution (140 ml) of methyl (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)benzo(b)furan-2-carboxylate (5.6 g) in methanol was added 2.0 M aqueous potassium hydroxide solution (100 ml) and the mixture was refluxed under heating for 2 hr. The reaction mixture was poured into water and the aqueous solution was made acidic (pH=1) with conc. hydrochloric acid. The solution was extracted with a mixed solvent of chloroform-methanol (2:1) and the oil layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was crystallized from ethyl acetate, and the crystals were collected by filtration and dried to give hydrochloride (4.7 g) of the title compound as pale-yellow crystals, melting point 234-235°C (decomposition).

Starting Material Synthesis Example 23

ethyl (S)-7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)benzo(b)furan-2-carboxylate

By the reactions in the same manner as in Starting Material Synthesis Example 11 using ethyl (S)-7-

(glycidyloxy)benzo(b)furan-2-carboxylate (5.3 g) and 4-(naphthalen-2-yl)piperidine (3.0 g), the title compound (5.2 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ:1.41(t, J=7.3, 3H), 1.87-1.98(m, 4H), 2.23(t, J=7.3, 1H), 2.25-2.63(m, 1H), 2.48-2.79(m, 4H), 3.05(d, J=10.7, 1H), 3.05(d, J=10.7, 1H), 3.23(d, J=10.7, 1H), 4.10-4.28(m, 3H), 4.45(q, J=7.3, 2H), 6.72(d, J=8.3, 1H), 7.21(d, J=8.3, 1H), 7.35-7.49(m, 4H), 7.67-7.70(m, 2H), 7.75-7.82(m, 3H)

Starting Material Synthesis Example 24

(S)-7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-benzo(b)furan-2-carboxylic acid

To a solution of ethyl (S)-7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)benzo(b)furan-2-carboxylate (5.2 g) in methanol (50 ml) was added 10% aqueous sodium hydroxide solution (50 ml) and the mixture was refluxed under heating for 1 hr. The reaction mixture was made acidic (pH 1) with conc. hydrochloric acid and extracted with chloroform. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure to give the title compound (4.0 g) as a brown oil.

^{1}H-NMR(DMSO-d_6)δ:1.81-2.20(m, 4H), 2.80-3.17(m, 2H), 4.01(dd, J=9.3, 3.4, 1H), 4.12(dd, J=9.3, 3.4, 1H), 6.75(d, J=8.3, 1H), 7.19(d, J=8.3, 1H), 7.48(t, J=8.3, 1H), 7.44-7.51(m, 3H), 7.77(s, 1H), 7.87-7.90(m, 3H), 8.04(s, 1H)

Starting Material Synthesis Example 25

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1H-indole-2-carboxylic acid

To a solution of ethyl 4-hydroxy-1H-indole-2-carboxylate (1.3 g) in DMF (50 ml) were added potassium carbonate and (S)-glycidyl nosylate (1.0 g) and the mixture was stirred one day. The reaction mixture was poured into water and extracted with ethyl acetate. The oil layer was washed with water and dried over anhydrous magnesium sulfate and the solvent was evaporated

under reduced pressure to give ethyl (S)-4-glycidyloxy-1H-indole-2-carboxylate (1.8 g) as a brown oil. This was dissolved in methanol (50 ml) and the solution was refluxed under heating with 4-(naphthalen-2-yl)piperidine (1.5 g) for 3 hr. The solvent was evaporated under reduced pressure to give ethyl (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1H-indole-2-carboxylate (1.4 g) as pale-brown crystals (melting point 115-117°C). By the reactions in the same manner as in Starting Material Synthesis Example 22, the title compound (1.1 g) was obtained as white crystals, melting point 171-173°C.

Starting Material Synthesis Example 26

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-methyl-indole-2-carboxylic acid

By the reactions in the same manner as in Starting Material Synthesis Example 25 using ethyl 4-hydroxy-1-methyl-indole-2-carboxylate (4.0 g) obtained in Starting Material Synthesis Example 9, (S)-glycidyl nosylate (4.5 g) and 4-(naphthalen-2-yl)piperidine (4.3 g), ethyl (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-(2-methylpropyl)-1-methyl-indole-2-carboxylate (5.8 g) was obtained. This was dissolved in ethanol (40 ml). Water (40 ml) and potassium hydroxide (4.5 g) were added, and the mixture was refluxed for 2.5 hr. From the obtained reaction mixture, ethanol was evaporated under reduced pressure and 1N aqueous hydrochloric acid solution (40 ml) was added under ice-cooling. The mixture was extracted with chloroform. The obtained oil layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and isopropyl ether was added to the obtained oil. The obtained crystals were collected by filtration to give the title compound (4.2 g) as pale-yellow crystals, melting point 158-161°C.

Starting Material Synthesis Example 27

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-(2-methylpropyl)-indole-2-carboxylic acid

By the reactions in the same manner as in Starting Material Synthesis Example 25 using ethyl 4-hydroxy-1-(2-methylpropyl)-indole-2-carboxylate (5.0 g) obtained in Starting Material Synthesis Example 12, (S)-glycidyl nosylate (4.5 g) and 4-(naphthalen-2-yl)piperidine (5.3 g), ethyl (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-(2-methylpropyl)-indole-2-carboxylate (7.5 g) was obtained. This was dissolved in ethanol (40 ml) and water (30 ml) and potassium hydroxide (4.0 g) were added. The mixture was refluxed for 2.5 hr. From the obtained reaction mixture, ethanol was evaporated under reduced pressure and 1N aqueous hydrochloric acid solution (30 ml) was added under ice-cooling. The mixture was extracted with chloroform. The obtained oil layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and isopropyl ether was added to the obtained oil. The obtained crystals were collected by filtration to give the title compound (6.7 g) as pale-yellow crystals.

^{1}H-NMR(CD_3OD)δ: 0.84-0.86(m, 7H), 2.15-2.23(m, 5H), 3.11-3.65(m, 4H), 3.65(m, 2H), 4.18-4.25(m, 2H), 4.40(d, J=7.3, 2H), 4.58(m, 1H), 6.60(d, J=7.8, 1H), 7.10(d, J=8.3, 1H), 7.24(dd, J=7.8, 8.3, 1H), 7.46-7.47(m, 4H), 7.74-7.86(m, 4H)

Starting Material Synthesis Example 28

1-hydroxyimino-1-(4-methoxybenzo(b)furan-2-yl)methylamine

To a solution (40 ml) of 4-methoxybenzo(b)furan-2-carbonitrile (2.8 g) in ethanol were added hydroxylamine hydrochloride (1.2 g) and sodium hydrogencarbonate (3.0 g). The mixture was refluxed under heating for 1.5 hr. The inorganic material was filtered off and the reaction mixture was concentrated under reduced pressure to give the title compound (3.4 g) as brown crystals.

^{1}H-NMR($CDCl_3$)δ:3.94(s, 3H), 6.68(d, J=7.8, 1H), 7.13(d, J=7.8, 1H), 7.19(s, 1H), 7.26(t, J=7.8,1H)

Starting Material Synthesis Example 29

3-(4-methoxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole

1-Hydroxyimino-1-(4-methoxybenzo(b)furan-2-yl)methylamine (3.4 g) was dissolved in acetic anhydride (40 ml) and the mixture was refluxed under heating for 14 hr. The reaction mixture was concentrated under reduced pressure and the obtained residue was recrystallized from acetonitrile to give the title compound (1.1 g) as pale-as brown crystals.

^{1}H-NMR($CDCl_3$)δ:2.68(s, 3H), 3.97(s, 3H), 6.70(d, J=8.3, 1H), 7.22(d, J=8.3, 1H), 7.33(t, J=8.3,1H), 7.58(s, 1H)

Starting Material Synthesis Example 30

3-(4-hydroxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 5 using 3-(4-methoxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole (1.1 g) and boron tribromide (4.2 ml), the title compound (0.75 g) was obtained as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:2.65(s, 3H), 6.68(d, J=7.8, 1H), 7.12(d, J=8.3, 1H), 7.23(dd, J=7.8, 8.3, 1H), 7.60(s, 1H), 10.30(s, 1H)

Starting Material Synthesis Example 31

(S)-3-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 3-(4-hydroxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole (0.75 g) and (S)-glycidyl nosylate (0.93 g), the title compound (0.45 g) was obtained as white crystals.

^{1}H-NMR($CDCl_3$)δ:2.69(s, 3H), 2.83(dd, J=4.9, 2.5, 1H), 2.96(t, J=4.9, 1H), 3.43-3.45(m, 1H), 4.13(dd, J=11.2, 4.4, 1H), 4.40(dd, J=11.2, 3.0, 1H), 6.71(d, J=7.8, 1H), 7.25(d, J=8.3, 1H), 7.32(dd, J=8.3, 7.8, 1H), 7.62(s, 1H)

Starting Material Synthesis Example 32

1-hydroxyimino-1-(7-methoxybenzo(b)furan-2-yl)methylamine

By the reactions in the same manner as in Starting Material Synthesis Example 18 using 7-methoxybenzo(b)furan-2-carbonitrile (3.0 g), hydroxylamine hydrochloride (1.4 g) and sodium hydrogencarbonate (2.1 g), the title compound (3.3 g) was obtained as brown crystals.

^{1}H-NMR(CD_3OD)δ:3.97(s, 3H), 6.89-6.91(m, 1H), 7.11-7.17(m, 3H)

Starting Material Synthesis Example 33

3-(7-methoxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 29 using 1-hydroxyimino-1-(7-methoxybenzo(b)furan-2-yl)methylamine (3.3 g), the title compound (1.7 g) was obtained as white crystals.

^{1}H-NMR($CDCl_3$)δ:2.68(s, 3H), 4.03(s, 3H), 6.90(d, J=7.8, 1H), 7.21(d, J=7.8, 1H), 7.25(t, J=7.8,1H), 7.45(s, 1H)

Starting Material Synthesis Example 34

3-(7-hydroxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 5 using 3-(7-methoxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole (1.7 g) and boron tribromide (6.5 ml), the title compound (1.5 g) was obtained as white crystals.

^{1}H-NMR(DMSO-d_6)δ:2.65(s, 3H), 6.68(d, J=7.8, 1H), 7.12(d, J=8.3, 1H), 7.23(dd, J=7.8, 8.3, 1H), 7.60(s, 1H), 10.30(s, 1H)

Starting Material Synthesis Example 35

(S)-3-(7-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 3-(7-hydroxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole (1.5 g) and (S)-glycidyl nosylate (1.8 g), the title compound (1.7 g) was obtained as white crystals.

^{1}H-NMR($CDCl_3$)δ:2.69(s, 3H), 2.81(dd, J=4.9, 2.4, 1H), 2.94(t, J=4.9, 1H), 3.46-3.48(m, 1H), 4.26(dd, J=11.2, 5.4, 1H),

4.46(dd, J=11.2, 3.4, 1H), 6.95(d, J=7.8, 1H), 7.21(t, J=7.8, 1H), 7.29(d, J=7.8, 1H), 7.46(s, 1H)

Starting Material Synthesis Example 36

N'-(4-methoxybenzo(b)furan-2-ylcarbonyl)acetohydrazide

To a solution (700 ml) of 4-methoxybenzo(b)furan-2-carboxylic acid (43.4 g) in THF was added 1,1'-carbonylbis-1H-imidazole (CDI) (38.4 g) and the mixture was stirred at room temperature for 1 hr. Acetohydrazine (17.6 g) was added to this reaction mixture, and the mixture was stirred for 1 more hr. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration and dried to give the title compound (38.4 g) as pale-brown crystals.
^{1}H-NMR(DMSO-d_6)δ:1.91(s, 3H), 3.93(s, 3H), 6.86(d, J=7.8, 1H), 7.25(d, J=7.8, 1H), 7.42(t, J=7.8, 1H), 7.61(s, 1H), 9.92(s, 1H), 10.46(s, 1H)

Starting Material Synthesis Example 37

2-(4-methoxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole

To a solution (400 ml) of N'-(4-methoxybenzo(b)furan-2-ylcarbonyl)acetohydrazide (15.6 g) in 1,2-dichloroethane were added triethylamine (21 ml) and triphenylphosphine (19.8 g) and the reaction temperature was set to 5°C. To this reaction mixture was added dropwise diethyl azodicarboxylate (40% toluene solution) (33 ml) over 15 min. The reaction temperature was set to room temperature and the mixture was stirred for 1.5 hr and washed with saturated aqueous solution of ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was concentrated under reduced pressure and purified by silica gel column chromatography (chloroform/ethyl acetate) to give the title compound (4.6 g) as pale-yellow crystals.
^{1}H-NMR($CDCl_3$)δ:2.65(s, 3H), 3.97(s, 3H), 6.72(d, J=8.3, 1H), 7.22(d, J=8.3, 1H), 7.36(t, J=8.3,1H), 7.56(s, 1H)

Starting Material Synthesis Example 38

2-(4-hydroxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 5 using 2-(4-methoxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole (6.5 g) and boron tribromide (27 ml), the title compound (3.3 g) was obtained as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:2.60(s, 3H), 6.71(d, J=8.3, 1H), 7.16(d, J=8.3, 1H), 7.29(t, J=8.3, 1H), 7.68(s, 1H)

Starting Material Synthesis Example 39

(S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 2-(4-hydroxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole (3.3 g) and (S)-glycidyl nosylate (3.7 g), the title compound (1.1 g) was obtained as white crystals.

^{1}H-NMR($CDCl_3$)δ:2.65(s, 3H), 2.83(dd, J=4.9, 2.4, 1H), 2.96(t, J=4.9, 1H), 3.43-3.46(m, 1H), 4.09(dd, J=11.2, 5.8, 1H), 4.42(dd, J=11.2, 2.9, 1H), 6.72(d, J=8.3, 1H), 7.23(d, J=8.3, 1H), 7.34(t, J=8.3, 1H), 7.59(s, 1H)

Starting Material Synthesis Example 40

2-(7-methoxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole

7-Methoxybenzo(b)furan-2-carboxylic acid (10 g) was dissolved in tetrahydrofuran (100 ml) and 1,1'-carbonylbis-1H-imidazole (CDI) (12.6 g) and acetohydrazine (4.0 g) were added. The mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily product (19 g). This oily product (19 g) was dissolved in 1,2-dichloroethane (300 ml) and triphenylphosphine (39 g) and triethylamine (25 ml) were added. The mixture was stirred under ice-cooling. Diisopropyl azodicarboxylate (40% toluene solution) (75 g) was added and then the mixture was stirred at

room temperature for 3 hr. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (8.0 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ:2.65(s, 3H), 4.05(s, 3H), 6.92(d, J=7.8, 1H), 7.23-7.28(m, 2H), 7.51(s, 1H)

Starting Material Synthesis Example 41

N'-(4-methoxymethyloxybenzo(b)thiophen-2-ylcarbonyl)-acetohydrazide

4-Methoxymethyloxybenzothiophene-2-carboxylic acid (7 g) was dissolved in tetrahydrofuran (100 ml) and CDI (7.3 g) and acetohydrazine (2.4 g) was added. The mixture was stirred at room temperature for 3 hr. The precipitated crystals were collected by filtration to give the title compound (3.9 g).

^{1}H-NMR(DMSO-d_6)δ:1.99(s, 3H), 3.32(bs, 2H), 3.51(s, 3H), 5.37(s, 2H), 7.03(d, J=7.8, 1H), 7.36(t, J=7.8, 1H), 7.52(d, J=7.8, 1H), 8.32(s, 1H)

Starting Material Synthesis Example 42

2-(4-methoxymethyloxybenzo(b)thiophen-2-yl)-5-methyl-1,3,4-oxadiazole

N'-(4-Methoxymethyloxybenzo(b)thiophen-2-ylcarbonyl)acetohydrazide (2.4 g) was dissolved in 1,2-dichloroethane (50 ml) and triphenylphosphine (3.2 g) and triethylamine (2 ml) were added. The mixture was stirred under ice-cooling. Diethyl azodicarboxylate (40% toluene solution) (5.2 g) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title product (1.4 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ:2.61(s, 3H), 3.54(s, 3H), 5.38(s, 2H), 7.05(d, J=7.8, 1H), 7.38(t, J=7.8, 1H), 7.52(d, J=7.8, 1H), 8.12(s, 1H)

Starting Material Synthesis Example 43

2-(4-hydroxybenzo(b)thiophen-2-yl)-5-methyl-1,3,4-oxadiazole

4-Methoxymethyloxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzothiophen (1.4 g) was dissolved in a mixed solvent (10 ml) of acetic acid - water (1:1) and the mixture was heated at 80°C for 4 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily compound (1.4 g).

^{1}H-NMR(DMSO-d_6)δ:2.61(s, 3H), 6.83(d, J=7.8, 1H), 7.32(t, J=7.8, 1H), 7.44(d, J=7.8, 1H), 8.07(s, 1H), 10.44(bs, 1H)

Starting Material Synthesis Example 44

N'-(4-benzyloxy-1H-indol-2-ylcarbonyl)acetohydrazide

Ethyl 4-benzyloxy-indol-2-carboxylate (10 g) was dissolved in dioxane - water (1:1)(200 ml) and potassium hydroxide (3.8 g) was added. The mixture was refluxed under heating for 2 hr. The reaction mixture was poured into ice water, made acidic with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 4-benzyloxy-indol-2-carboxylic acid as pale-yellow crystals (9.0 g). The crystals were dissolved in dimethylformamide (100 ml) and WSC (7.6 g), HOBt (6.9 g), triethylamine (7.0 ml) and acetohydrazine (2.6 g) were added thereto. The mixture was stirred at room temperature for 6 hr.

The reaction mixture was poured into ice water and the precipitated crystals were collected by filtration to give the title compound (10 g).

^{1}H-NMR(DMSO-d_6)δ:1.93(s, 3H), 5.22(s, 2H), 6.62(d, J=7.8, 1H), 7.04(d, J=7.8, 1H), 7.11(t, J=7.8, 1H), 7.36-7.45(m, 5H), 7.54(s, 1H), 9.85(s, 1H), 10.20(s, 1H), 11.67(s, 1H)

Starting Material Synthesis Example 45

4-benzyloxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indole

N'-(4-Benzyloxy-1H-indol-2-ylcarbonyl)acetohydrazide (7.5 g) was dissolved in tetrahydrofuran (250 ml) and triphenylphosphine (9.0 g) and triethylamine (6 ml) were added. The mixture was stirred under ice-cooling. Diisopropyl azodicarboxylate (40% toluene solution) (17.7 g) was added and the mixture was stirred at 50°C for 2 hr. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (6.0 g) as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:2.59(s, 3H), 5.25(s, 2H), 6.65(d, J=7.8, 1H), 7.07(d, J=7.8, 1H), 7.15(m, 2H), 7.34(m, 1H), 7.41(m, 2H), 7.53(m, 2H), 12.21(s, 1H)

Starting Material Synthesis Example 46

N'-(7-methoxybenzo(b)furan-2-ylcarbonyl)benzohydrazide

7-Methoxybenzo(b)furan-2-ylcarbohydrazide (10 g) was dissolved in dichloromethane (100 ml) and triethylamine (9.0 ml) and benzoyl chloride (7.8 g) were added thereto. The mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (5.0 g) as white crystals.

^{1}H-NMR(DMSO-d_6)δ:4.00(s, 3H), 7.08(d, J=7.8, 1H), 7.27(t, J=7.8, 1H), 7.35(d, J=7.8, 1H), 7.47-7.60(m, 3H), 7.68(s, 1H), 7.94(m, 2H), 10.57(s, 1H), 10.76(s, 1H)

Starting Material Synthesis Example 47

2-(7-methoxybenzo(b)furan-2-yl)-5-phenyl-1,3,4-oxadiazole

N'-(7-Methoxybenzo(b)furan-2-ylcarbonyl)benzohydrazide

(5.0 g) was dissolved in thionyl chloride (20 ml) and the mixture was stirred with heating at 80°C for 1 hr. Thionyl chloride was evaporated under reduced pressure and water was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound (3.7 g) as pale-yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:4.02(s, 3H), 7.12(d, J=7.8, 1H), 7.29(t, J=7.8, 1H), 7.38(d, J=7.8, 1H), 7.63-7.68(m, 3H), 7.88(s, 1H), 8.13(m, 2H)

Starting Material Synthesis Example 48

N'-(4-methoxybenzo(b)furan-2-ylcarbonyl)trifluoroacetohydrazide

To a solution (250 ml) of 4-methoxybenzo(b)furan-2-ylcarbohydrazide (9.5 g) in methylene chloride was added trifluoroacetic anhydride (8.5 ml), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from hexane. The crystals were collected by filtration and dried to give the title compound (10.5 g) as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:3.94(s, 3H), 6.89(d, J=8.3, 1H), 7.28(d, J=8.3, 1H), 7.45(t, J=8.3, 1H), 7.66(s, 1H), 11.04(s, 1H), 11.70(s, 1H)

Starting Material Synthesis Example 49

2-(4-methoxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 37 using N'-(4-methoxybenzo(b)furan-2-ylcarbonyl)trifluoroacetohydrazide (5.2 g), triethylamine (7.2 ml), triphenylphosphine (9.0 g) and diethyl azodicarboxylate (40% toluene solution, 6.2 ml), the title compound (4.0 g) was obtained as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ:3.98(s, 3H), 6.71(d, J=8.3, 1H), 7.18(d, J=8.3, 1H), 7.48(t, J=8.3,1H), 7.95(s, 1H)

Starting Material Synthesis Example 50

2-(4-hydroxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 5 using 2-(4-methoxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole (4.0 g) and boron tribromide (15 ml), the title compound (3.6 g) was obtained as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:6.73(d, J=8.3, 1H), 7.22(d, J=8.3, 1H), 7.36(t, J=8.3, 1H), 10.52(s, 1H)

Starting Material Synthesis Example 51

(S)-(2-(4-glycidyloxybenzo(b)furan-2-yl)-5-trifluoromethyl-1;3,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 2-(4-hydroxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole (3.3 g) and (S)-glycidyl nosylate (3.7 g), the title compound (1.1 g) was obtained as white crystals.

^{1}H-NMR($CDCl_3$)δ:2.83(dd, J=4.9, 2.4, 1H), 2.99(t, J=4.9, 1H), 3.44-3.46(m, 1H), 4.12(dd, J=11.2, 5.9, 1H), 4.44(dd, J=11.2, 2.9, 1H), 6.76(d, J=8.3, 1H), 7.27(d, J=8.3, 1H), 7.42(t, J=8.3, 1H), 7.83(s, 1H)

Starting Material Synthesis Example 52

N'-(7-methoxybenzo(b)furan-2-ylcarbonyl)trifluoroacetohydrazide

To a solution (300 ml) of 7-methoxybenzo(b)furan-2-ylcarbohydrazide (14.0 g) in methylene chloride was added trifluoroacetic anhydride (11.5 ml) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from hexane, collected by filtration and dried to give the title compound (16.1 g) as white crystals.

^{1}H-NMR(DMSO-d_6)δ:7.11(d, J=7.8, 1H), 7.28(t, J=7.8, 1H), 7.35(d, J=7.8, 1H), 7.69(s, 1H), 11.10(s, 1H)

Starting Material Synthesis Example 53

2-(7-methoxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole

To a solution (280 ml) of N'-(1,1,1-trifluoroaceto)-N'-(7-methoxybenzo(b)furan-2-yl) carbohydrazide (14.6 g) in 1,2-dichloroethane were added thionyl chloride (4.2 ml) and DMF (0.1 ml) and the mixture was refluxed under heating for 4.5 hr. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (chloroform/ethyl acetate) to give the title compound (2.4 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ:4.06(s, 3H), 6.99(d, J=6.9, 1H), 7.22(d, J=6.9, 1H), 7.26-7.31(m, 2H), 7.72(s, 1H)

Starting Material Synthesis Example 54

2-(7-hydroxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 5 using 2-(7-methoxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole (2.4 g) and boron tribromide (5.0 ml), the title compound (2.2 g) was obtained as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:6.96(d, J=7.3, 1H), 7.19(t, J=7.3, 1H), 7.29(t, d=7.3, 1H), 8.00(s, 1H), 10.50(s, 1H)

Starting Material Synthesis Example 55

(S)-2-(7-glycidyloxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 2-(7-hydroxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole (2.4 g) and (S)-glycidyl nosylate (2.2 g), the title compound (1.0 g) was obtained as white crystals.

^{1}H-NMR($CDCl_3$)δ:2.81-2.85(m, 1H), 2.96-2.98(m, 1H), 3.42-3.50(m, 1H), 4.23(dd, J=11.2, 5.8, 1H), 4.52(dd, J=11.2, 3.4, 1H), 7.04(d, J=7.8, 1H), 7.30(t, J=7.8, 1H), 7.33(d, J=7.8, 1H), 7.71(s, 1H)

Starting Material Synthesis Example 56

5-(4-methoxybenzo(b)furan-2-yl)-3-methyl-1,2,4-oxadiazole

To a solution (50 ml) of 4-methoxybenzo(b)furan-2-carboxylic acid (1.9 g) in THF were added thionyl chloride (0.9 ml) and DMF (0.1 ml), and the mixture was refluxed under heating for 20 min. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in pyridine (50 ml) and acetamide oxime hydrochloride (1.3 g) was added. The mixture was refluxed under heating for 1 hr and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:ethyl acetate=6:1) to give the title compound (1.0 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ:2.51(s, 3H), 3.98(s, 3H), 6.73(d, J=7.8, 1H), 7.24(d, J=8.3, 1H), 7.38(dd, J=7.8,8.3,1H), 7.73(s, 1H)

Starting Material Synthesis Example 57

5-(4-hydroxybenzo(b)furan-2-yl)-3-methyl-1,2,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 5 using 5-(4-methoxybenzo(b)furan-2-yl)-3-methyl-1,2,4-oxadiazole (0.98 g) and boron tribromide (3.1 ml), the title compound (0.72 g) was obtained as yellow crystals.

^{1}H-NMR(CD_3OD)δ:2.44(s, 3H), 6.69(d, J=8.3, 1H), 7.10(d, J=8.3, 1H), 7.31(t, J=8.3, 1H), 7.79(s, 1H)

Starting Material Synthesis Example 58

(S)-5-(4-glycidyloxybenzo(b)furan-2-yl)-3-methyl-1,2,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 2-(4-hydroxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole (3.3 g) and (S)-glycidyl nosylate

(3.7 g), the title compound (1.1 g) was obtained as white crystals.

^{1}H-NMR($CDCl_3$)δ:2.51(s, 3H), 2.83(dd, J=4.8, 2.4, 1H), 2.96(t, J=4.8, 1H), 3.42-3.46(m, 1H), 4.11(dd, J=11.2, 5.8, 1H), 4.42(dd, J=11.2, 2.9, 1H), 6.73(d, J=8.3, 1H), 7.26(d, J=8.3, 1H), 7.39(t, J=8.3, 1H), 7.78(s, 1H)

Starting Material Synthesis Example 59

methyl 4-hydroxybenzo(b)thiophene-2-carboxylate

4-Methoxymethyloxybenzo(b)thiophene-2-carboxylic acid (7 g) was dissolved in methanol (140 ml) and thionyl chloride (2.0 ml) was added under ice-cooling. The mixture was refluxed under heating for 2 hr and the reaction mixture was concentrated under reduced pressure. Water was added and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure to give the title compound (6.0 g).

^{1}H-NMR($CDCl_3$):3.95(s, 3H), 6.82(d, 1H, J=4.8), 7.23-7.38(m, 2H), 8.30(s, 1H)

Starting Material Synthesis Example 60

5-(4-hydroxybenzo(b)thiophen-2-yl)-3-methyl-1,2,4-oxadiazole

Methyl 4-hydroxybenzo(b)thiophene-2-carboxylate (6.0 g) was dissolved in dimethylformamide (80 ml) and sodium hydride (1.7 g) was added under ice-cooling. The mixture was stirred for 30 min and chloromethyl methyl ether (3 g) was added. The mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure. Tetrahydrofuran (100 ml) was added and the reaction mixture was ice-cooled, and sodium hydride (1.6 g) and acetamide oxime (3.0 g) were added in the presence of molecular sieves (4A). The mixture was refluxed under heating for 30 min and the tetrahydrofuran solution obtained earlier was added to

the solution. The mixture was refluxed under heating for 1 hr, and after cooling, poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure. Thereto were added tetrahydrofuran (35 ml) and 6N hydrochloric acid (20 ml), and the mixture was stirred at 50°C for 30 min. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure to give the title compound (2.4 g).

^{1}H-NMR($CDCl_3$):2.50(s, 3H), 5.70(bs, 1H), 6.78(d, 1H, J=7.6), 7.34(t, 1H, J=7.8), 7.47(d, 1H, J=8.3), 8.33(s, 1H)

Starting Material Synthesis Example 61

(S)-5-(4-glycidyloxybenzo(b)thiophen-2-yl)-3-methyl-1,2,4-oxadiazole

Synthesized according to a method similar to the method of Starting Material Synthesis Example 1.

^{1}H-NMR($CDCl_3$):2.48(s, 3H), 2.83(dd, 1H, J=2.4,4.9), 2.98(t, 1H, J=4.4), 3.42-3.48(m, 1H), 4.14(dd, 1H, J=5.9,11.3), 4.41(dd, 1H, J=3.0,10.8), 6.80(d, 1H, J=7.8), 7.40(t, 1H, J=7.8), 7.48(d, 1H, J=8.3), 8.35(s, 1H)

Starting Material Synthesis Example 62

1-(4-methoxybenzo(b)furan-2-yl)butan-1,3-dione

2-Acetyl-4-methoxybenzo(b)thiophene (2.4 g) was dissolved in ethyl acetate (50 ml), and sodium hydride (1.5 g) was added under ice-cooling. The mixture was stirred at room temperature for 10 min, and the mixture was refluxed under heating for 1 hr. After cooling, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (0.7 g).

^{1}H-NMR($CDCl_3$):2.21(s, 3H), 3.96(s, 3H), 6.25(s, 1H), 6.68(d, 1H, J=7.8), 6.68(d, 1H, J=7.6), 7.15(d, 1H, J=7.8), 7.33(t, 1H, J=7.8), 7.56(s, 1H)

Starting Material Synthesis Example 63

(S)-3-(4-glycidyloxybenzo(b)furan-2-yl)-1,5-dimethylpyrazole

1-(4-Methoxybenzo(b)furan-2-yl)butan-1,3-dione (1.0 g) was dissolved in methanol (30 ml) and methylhydrazine (0.3 g) was added thereto. The mixture was refluxed under heating for 20 min. The reaction solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/acetone). To the obtained oil was added methylene chloride (30 ml), and the mixture was cooled to -40°C, and boron tribromide (1 ml) was added dropwise. After the completion of the reaction, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure to give 3-(4-hydroxybenzo(b)furan-2-yl)-1,5-dimethylpyrazole (0.85 g) as a brown oil. Using this and (S)-glycidyl nosylate (0.75 g) and in the same manner as in Starting Material Synthesis Example 1, the title compound (0.53 g) was obtained as a brown oil.
^{1}H-NMR($CDCl_3$):2.33(s, 3H), 2.82(dd, 1H, J=2.8, 4.8), 2.94(t, 1H, J=4.4), 3.86(s, 3H), 4.13(dd, 1H, J=5.4,11.2), 4.36(dd, 1H, J=3.4, 11.2), 6.40(s, 1H), 6.65(d, 1H, J=6.3), 7.06(s, 1H), 7.08-7.12(m, 2H)

Starting Material Synthesis Example 64

7-methoxybenzo(b)furan-2-carboxylic acid

To acetone (300 ml) were added o-vanillin (70 g), ethyl bromoacetate (50 g) and potassium carbonate (70 g) and the mixture was stirred under heating for 5 hrs. After cooling, the mixture was poured into water and the precipitated crystals were collected by filtration. After drying, the crystals were dissolved in dimethylformamide (500 ml). To the solution was added 1,8-diazabicyclo(5,4,0)undec-7-en (DBU, 50 ml) and the

mixture was stirred under heating at 110°C for 30 min. After cooling, the mixture was added to water. The resultant crystals were collected by filtration. Drying, gave ethyl ester of the title compound (56 g). The crystals (25 g) were dissolved in ethanol (50 ml), and aqueous potassium hydroxide solution (22 g/100 ml) was added to the solution. The solution was stirred at 40°C for 10 min. After cooling, the solution was acidified with hydrochloric acid and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give the title compound (15 g). m.p. 212-214°C.

Starting Material Synthesis Example 65

2-(7-hydroxybenzo(b)furan-2-yl)-5-methyloxazole

7-Methoxybenzo(b)furan-2-carboxylic acid (6.0 g) was dissolved in chloroform (30 ml), and dimethylformamide (1 ml) was added. Thionyl chloride (4.0 ml) was added, and the mixture was stirred with heating at 50°C for 2 hr. The reaction solvent was evaporated under reduced pressure, and tetrahydrofuran (100 ml) was added. The mixture was cooled and a solution of propargylamine (1.65 g) and triethylamine (12 ml) in tetrahydrofuran was added dropwise with stirring. The mixture was stirred at room temperature for 2 hr, and poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure. This product (4 g) was dissolved in acetic acid (40 ml) and mercury(II) acetate (0.5 g) was added. The mixture was refluxed for 2 hr. After cooling, acetic acid was evaporated under reduced pressure and aqueous potassium carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure to give pale-yellow crystals (1.5 g). The crystals

were dissolved in methylene chloride (30 ml), and the mixture was cooled to -20°C. Boron tribromide (0.8 ml) was added dropwise and the mixture was stirred at 0°C for 1 hr. The reaction mixture was poured into water, and extracted with tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate, and after filtration, the solvent was evaporated under reduced pressure to give the title compound (1.0).

^{1}H-NMR(DMSO-d_6):2.42(s, 3H), 6.92-6.95(m, 2H), 7.01-7.13(m, 1H), 7.18-7.35(m, 1H), 7.63(d, 1H, J=2.8)

Starting Material Synthesis Example 66

5-(7-methoxybenzo(b)furan-2-yl)-3-methylisoxazole

Thionyl chloride (10 ml) was added dropwise to methanol (100 ml) with stirring under ice-cooling. 7-Methoxybenzo(b)furan-2-carboxylic acid (10 g) was successively added, and the mixture was refluxed under heating for 1 hr. After cooling, the solvent was evaporated under reduced pressure and the precipitated yellow crystals were collected by filtration to give methyl 7-methoxybenzo(b)furan-2-carboxylate (11.2 g). This was used in the next reaction without purification. Acetone oxime (4.8 g) was dissolved in tetrahydrofuran (100 ml), and butyllithium (1.6M hexane solution) (80 ml) was added dropwise to this solution at -5°C with stirring. Thereafter, the mixture was stirred under ice-cooling for 1 hr, and a solution (50 ml) of methyl 7-methoxybenzo(b)furan-2-carboxylate (11.2 g) in tetrahydrofuran was added. The mixture was stirred at room temperature for 20 hr. A solution of sulfuric acid (28 g) dissolved in tetrahydrofuran (120 ml) - water (30 ml) was prepared, into which the reaction mixture was poured. The mixture was refluxed under heating for 2 hr. After cooling, the reaction mixture was poured into ice water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue was

purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (2.1 g).

^{1}H-NMR($CDCl_3$) δ: 2.38 (s, 3H), 4.04 (s, 3H), 6.57 (s, 1H), 6.88 (d, J=7.8, 1H), 7.22 (m, 3H)

Starting Material Synthesis Example 67

4-(4-methoxybenzo(b)furan-2-yl)-2-methylthiazole

To a solution (30 ml) of (4-methoxybenzo(b)furan-2-yl)-α-bromomethyl ketone (2.7 g) in ethanol was added thioacetamide (0.75 g), and the mixture was refluxed under heating for 6 hr. The precipitated crystals were collected by filtration and dried to give the title compound (2.7 g) as pale-brown crystals.

^{1}H-NMR(DMSO-d_6) δ: 2.72 (s, 3H), 3.91 (s, 3H), 6.81 (d, J=7.3, 1H), 7.13 (s, 1H), 7.21 (d, J=7.3, 1H), 7.27 (t, J=7.3, 1H), 7.90 (s, 1H)

Starting Material Synthesis Example 68

2-(2'-hydroxystyryl)-5-methyl-1,3,4-oxadiazole

2-Methoxymethyloxycinnamic acid (4.0 g) and CDI (3.1 g) were successively added to tetrahydrofuran (40 ml) and the mixture was stirred. One hour later, acetylhydrazide (1.4 g) was added, and the mixture was stirred for 3 more hr. The reaction mixture was poured into water and extracted with ethyl acetate to give an oil (3.5 g). This oil was dissolved in dichloroethane (300 ml) and triphenylphosphine (5 g) and triethylamine (3.3 ml) were added to this solution. Then DEAD (8.3 g) was added under ice-cooling. The mixture was stirred at room temperature for 2 hr, and aqueous potassium carbonate solution was added, and reaction mixture was extracted with chloroform. The organic solvent was dried and concentrated, and the residue was purified by silica gel chromatography (hexane/acetone) to give an oil (2.2 g). This oil was stirred with heating in a mixed solvent of water (20 ml) and hydrochloric acid (20 ml) for 2 hr, and after cooling, poured into water. The mixture was extracted with ethyl acetate to

give the title compound (1.5 g) as a brown oil.

^{1}H-NMR($CDCl_3$):2.58(s, 3H), 6.45(bs, 1H), 6.90(t, J=7.8,1H), 6.98(d, J=7.5,1H), 7.19(d, J=7.5,1H), 7.40(t, J=8.0,1H), 7.42(d, J=15.8,1H), 7.68(d, J=15.8,1H)

Starting Material Synthesis Example 69

2-(2'-hydroxystyryl)benzothiazole

Salicylaldehyde (6.1 g) and 2-methylthiazole (7.5 g) were mixed and conc. hydrochloric acid (1.5 ml) was added thereto. The mixture was stirred with heating at 100°C for 9 hr. The reaction mixture was cooled, and aqueous potassium hydroxide solution was added. The aqueous layer was washed with ether and made acidic with hydrochloric acid and extracted again with ethyl acetate. The organic solvent was dried and concentrated to give the title compound (2.5 g) as pale-yellow crystals, melting point 235-236°C.

Starting Material Synthesis Example 70

5-(2'-hydroxystyryl)-3-methyl-1,2,4-oxadiazole

Acetamide oxime (7.5 g), molecular sieves (4A) (10 g) and sodium hydride (5 g) were added to tetrahydrofuran (200 ml) and the mixture was refluxed under heating. To this reaction mixture was added dropwise ethyl 2-methoxymethyloxycinnamate (12 g) and the mixture was continuously heated for 2 hr. After cooling, the mixture was poured on ice and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure. Thereto were added tetrahydrofuran (10 ml) and 6N hydrochloric acid (20 ml) and the mixture was stirred with heating at 50°C for 30 min to allow precipitation of crystals. The crystals were collected by filtration and dried to give the title compound (6.0 g) as white crystals, melting point 184-186°C.

Starting Material Synthesis Example 71

(S)-4-glycidyloxybenzo(b)furan-2-ylmethylketone

To a suspension (40 ml) of sodium hydride (0.22 g) in DMF was added dropwise a solution (10 ml) of 4-

hydroxybenzo(b)furan-2-yl methyl ketone (0.80 g) in DMF under ice-cooling and the mixture was stirred at room temperature for 30 min. To this reaction mixture was added dropwise a solution (10 ml) of (S)-glycidyl nosylate (1.4 g) in DMF under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.61 g) as yellow crystals.

^{1}H-NMR($CDCl_3$):2.60(s, 3H), 2.82(dd, J=4.4, 5.9, 1H), 2.97(t, J=4.4, 1H), 3.43-3.46(m, 1H), 4.09(dd, J=10.8, 5.9, 1H), 4.42(dd, J=10.8, 3.0, 1H), 6.69(d, J=7.8,1H), 7.20(d, J=8.3, 1H), 7.39(t, J=8.3, 1H), 7.65(s, 1H)

Starting Material Synthesis Example 72

(S)-4-glycidyloxy-3-methylbenzo(b)furan-2-ylmethylketone

To a suspension (60 ml) of sodium hydride (1.4 g) in DMF was added dropwise a solution (30 ml) of 4-hydroxy-3-methylbenzo(b)furan-2-ylmethylketone (6.1 g) in DMF under ice-cooling and the mixture was stirred at room temperature for 30 min. To this reaction mixture was added dropwise under ice-cooling a solution (30 ml) of (S)-glycidyl nosylate (9.1 g) in DMF, and the mixture was stirred for 2 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (3.1 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$):2.59(s, 3H), 2.79(s, 3H), 2.83(dd, J=4.9, 2.3, 1H), 2.96(t, J=4.3, 1H), 3.43-3.45(m, 1H), 4.08(dd, J=11.2, 5.4, 1H), 4.37(dd, J=11.2, 3.0, 1H), 6.62(d, J=7.8,1H), 7.11(d, J=8.3, 1H), 7.34(t, J=8.3, 1H)

Starting Material Synthesis Example 73

N'-(4-methoxybenzo(b)furan-2-ylcarbonyl)propionohydrazide

To a solution (200 ml) of (4-methoxybenzo(b)furan-2-ylcarbonyl)hydrazide (8.5 g) in THF was added propionic anhydride (8.1 g) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from diisopropyl ether, collected by filtration and dried to give the title compound (8.3 g) as brown crystals.

^{1}H-NMR(DMSO-d_6)δ:1.05(t, J=7.8,3H), 2.19(q, J=7.8,2H), 3.93(s, 3H), 6.86(d, J=7.8, 1H), 7.25(d, J=8.3, 1H), 7.41(t, J=8.3, 1H), 7.62(s, 1H), 9.89(s, 1H), 10.46(s, 1H)

Starting Material Synthesis Example 74

2-(4-methoxybenzo(b)furan-2-yl)-5-ethyl-1,3,4-oxadiazole

N'-(4-Methoxybenzo(b)furan-2-ylcarbonyl)-propionohydrazide (8.3 g) obtained in Starting Material Synthesis Example 73 was added to phosphorus oxychloride (60 ml) and the mixture was stirred at 90°C for 1 hr. After cooling, the reaction mixture was poured into ice water and extracted with ethyl acetate. After washing with water, the oil layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (4.5 g) as yellow crystals.

^{1}H-NMR($CDCl_3$)δ:1.46(t, J=7.8,3H), 2.99(q, J=7.8,2H), 3.97(s, 3H), 6.72(d, J=7.8, 1H), 7.22(d, J=8.3, 1H), 7.36(t, J=8.3, 1H), 7.57(s, 1H)

Starting Material Synthesis Example 75

2-(4-hydroxybenzo(b)furan-2-yl)-5-ethyl-1,3,4-oxadiazole

To a solution (60 ml) of 2-(4-methoxybenzo(b)furan-2-yl)-5-ethyl-1,3,4-oxadiazole (4.5 g) obtained in Starting Material Synthesis Example 74 in methylene chloride was added boron tribromide (11.8 ml), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into ice water and stirred for 1 hr and extracted with a mixed solvent

of chloroform - methanol (2:1). After washing with water, the oil layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (3.1 g) as pale-yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:1.33(t, J=7.8,3H), 2.96(q, J=7.8, 2H), 6.71(d, J=8.3,1H), 7.16(d, J=8.8, 1H), 7.29(t, J=8.3, 1H), 7.69(s, 1H), 10.37(s, 1H)

Starting Material Synthesis Example 76

(S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-ethyl-1,3,4-oxadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 2-(4-hydroxybenzo(b)furan-2-yl)-5-ethyl-1,3,4-oxadiazole (3.1 g) obtained in Starting Material Synthesis Example 75, (S)-glycidyl nosylate (3.5 g) and potassium carbonate (5.6 g), the title compound (3.8 g) was obtained as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ:1.47(t, J=7.8,3H), 2.83(dd, J=3.9, 2.4, 1H), 2.96(t, J=3.9,1H), 2.99(q, J=7.8, 2H), 3.42-3.48(m, 1H), 4.11(dd, J=11.3,5.9, 1H), 4.42(dd, J=11.3, 3.0, 1H), 6.72(d, J=8.3, 1H), 7.25(d, J=8.3, 1H), 7.32(t, J=8.3, 1H), 7.61(s, 1H)

Starting Material Synthesis Example 77

5-(4-methoxybenzo(b)furan-2-yl)-3-methylisoxazole

To a solution (160 ml) of acetone oxime (5.0 g) in THF was added dropwise n-butyllithium (1.6 M hexane solution) over 15 min under ice-cooling and the mixture was stirred for 1 hr. Thereto was added dropwise a solution (60 ml) of methyl 4-methoxybenzo(b)furan-2-carboxylate (6.7 g) in THF and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into ice water, and conc. sulfuric acid (4 ml) was added carefully. The mixture was stirred for 20 min more. The aqueous layer was neutralized with sodium hydrogencarbonate and extracted with ethyl acetate. After washing with water, the oil layer was dried over anhydrous magnesium sulfate and the solvent was concentrated under

reduced pressure to give the title compound (3.0 g) as yellow crystals.

^{1}H-NMR($CDCl_3$)δ:2.38(s, 3H), 3.96(s, 3H), 6.46(s, 1H), 6.69(d, J=7.8, 1H), 7.15(d, J=8.3, 1H), 7.29(t, J=8.3, 1H), 7.32(s, 1H)

Starting Material Synthesis Example 78

5-(4-hydroxybenzo(b)furan-2-yl)-3-methylisoxazole

By the reactions in the same manner as in Starting Material Synthesis Example 5 using 5-(4-methoxybenzo(b)furan-2-yl)-3-methylisoxazole (3.0 g) and boron tribromide (7.6 ml), the title compound (2.6 g) was obtained as pale-yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:2.30(s, 3H), 6.68(d, J=7.8, 1H), 6.85(s, 1H), 7.10(d, J=8.3, 1H), 7.22(t, J=8.3, 1H), 7.49(s, 1H)

Starting Material Synthesis Example 79

(S)-5-(4-glycidyloxybenzo(b)furan-2-yl)-3-methylisoxazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 5-(4-hydroxybenzo(b)furan-2-yl)-3-methylisoxazole (2.6 g), (S)-glycidyl nosylate (3.1 g) and potassium carbonate (5.0 g), the title compound (2.8 g) was obtained as brown crystals.

^{1}H-NMR($CDCl_3$)δ:2.82(dd, J=4.9, 2.4, 1H), 2.96(t, J=4.9,1H), 3.43-3.46(m, 1H), 4.11(dd, J=11.2, 5.4, 1H), 4.39(dd, J=11.2, 3.0, 1H), 6.49(s, 1H), 6.70(d, J=8.3, 1H), 7.17(d, J=8.3, 1H), 7.28(t, J=8.3, 1H), 7.36(s, 1H)

Starting Material Synthesis Example 80

2-(4-methoxybenzo(b)furan-2-yl)-5-methyl-1,3,4-thiadiazole

To a solution (50 ml) of N'-(4-methoxybenzo(b)furan-2-ylthiocarbonyl)acetohydrazide (1.1 g) in toluene was added methanesulfonic acid (1.0 ml) and the mixture was stirred at 80°C for 30 min. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate and aqueous potassium carbonate solution. After washing with water, the oil layer was dried over anhydrous magnesium sulfate and the solvent was concentrated under reduced pressure to give the title compound (0.82 g) as yellow crystals.

^{1}H-NMR($CDCl_3$)δ:2.85(s, 3H), 3.97(s, 3H), 6.70(d, J=7.8, 1H), 7.18(d, J=8.3, 1H), 7.32(t, J=8.3, 1H), 7.57(s, 1H)

Starting Material Synthesis Example 81

2-(4-hydroxybenzo(b)furan-2-yl)-5-methyl-1,3,4-thiadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 5 using 2-(4-methoxybenzo(b)furan-2-yl)-5-methyl-1,3,4-thiadiazole (0.98 g) and boron tribromide (2.3 ml), the title compound (0.89 g) was obtained as pale-yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:2.80(s, 3H), 6.70(d, J=7.3, 1H), 7.13(d, J=8.3, 1H), 7.25(t, J=8.3, 1H), 7.67(s, 1H)

Starting Material Synthesis Example 82

(S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-thiadiazole

By the reactions in the same manner as in Starting Material Synthesis Example 1 using 2-(4-hydroxybenzo(b)furan-2-yl)-5-methyl-1,3,4-thiadiazole (1.1 g), (S)-glycidyl nosylate (1.2 g) and potassium carbonate (3.0 g), the title compound (1.0 g) was obtained as yellow crystals.

^{1}H-NMR($CDCl_3$)δ:2.82(dd, J=4.9, 3.0, 1H), 2.96(t, J=4.9,1H), 3.42-3.46(m, 1H), 4.13(dd, J=10.8, 5.9, 1H), 4.40(dd, J=10.8, 3.0, 1H), 6.71(d, J=7.8, 1H), 7.20(d, J=8.3, 1H), 7.31(t, J=8.3, 1H), 7.61(s, 1H)

Starting Material Synthesis Example 83

N-propargyl-4-methoxybenzo(b)furan-2-carboxamide

4-Methoxybenzo(b)furan-2-carboxylic acid (44.0 g) and propargylamine (12 g) were dissolved in dimethylformamide (200 ml), and WSC (48.0 g), 1-hydroxybenzotriazole hydrochloride (HOBt) (43.0 g) and triethylamine (50 ml) were added thereto at room temperature. The mixture was stirred for 4 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The oil layer was washed with saturated aqueous solution of ammonium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the

title compound as yellow crystals (45.0 g).

^{1}H-NMR($CDCl_3$)δ:3.32(s, 1H), 3.92(s, 3H), 4.06(m, 2H), 6.65(d, J=7.8, 1H), 7.18(d, J=7.8, 1H), 7.26(t, J=7.8, 1H), 7.36(s, 1H), 8.86(m, 1H)

Starting Material Synthesis Example 84

2-(4-methoxybenzo(b)furan-2-yl)-5-methyloxazol

To a solution (200 ml) of N-propargyl-4-methoxybenzo(b)furan-2-carboxamide (45.0 g) obtained in Starting Material Synthesis Example 83 in acetic acid was added mercury acetate (7.0 g), and the mixture was refluxed under heating for 3 hr. After cooling, the solvent was concentrated under reduced pressure and water was added. The mixture was neutralized with potassium carbonate and extracted with ethyl acetate. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform) to give the title compound (15.0 g) as yellow crystals.

^{1}H-NMR($CDCl_3$)δ:2.42(s, 3H), 3.96(s, 3H), 6.70(d, J=7.8, 1H), 6.90(s, 1H), 7.20(d, J=7.8, 1H), 7.29(t, J=7.8, 1H), 7.38(s, 1H)

Starting Material Synthesis Example 85

2-(4-hydroxybenzo(b)furan-2-yl)-5-methyloxazole

To a solution (100 ml) of 4-methoxy-2-(5-methyl-1,3-oxazol-2-yl)benzo(b)furan (15.0 g) obtained in Starting Material Synthesis Example 83 in dichloromethane was added dropwise boron tribromide (14 ml) under ice-cooling. The mixture was stirred at room temperature for 3 hr and poured into ice water. The mixture was stirred at room temperature for 3 more hr. The crystals were collected by filtration and dissolved in ethyl acetate. 1N HCl was added and the mixture was stirred one day. The organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound (11.0 g) as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ:2.41(s, 3H), 6.68(d, J=7.8, 1H), 7.04(s, 1H), 7.10(d, J=7.8, 1H), 7.21(t, J=7.8, 1H), 7.45(s, 1H), 10.17(bs, 1H)

The structural formulas of the compounds obtained in Starting Material Synthesis Examples are shown in the following.

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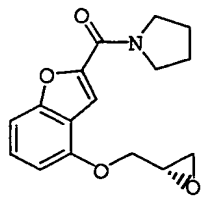

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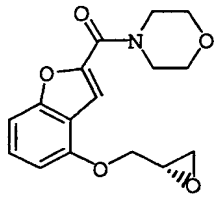

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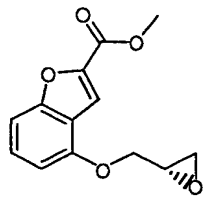

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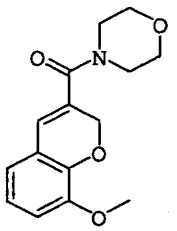

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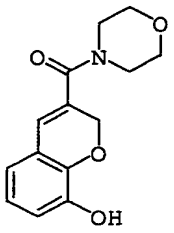

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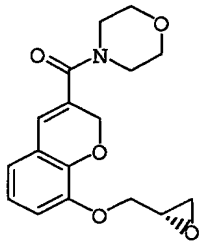

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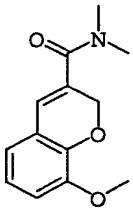

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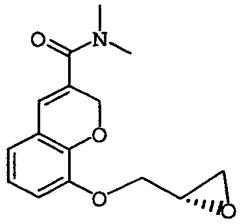

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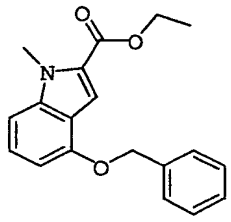

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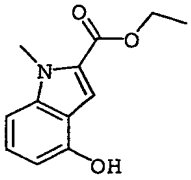

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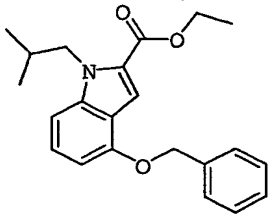

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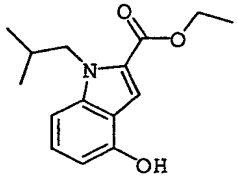

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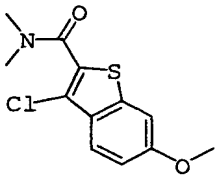

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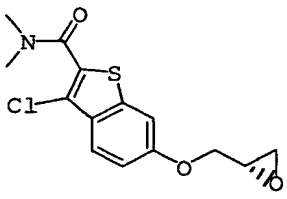

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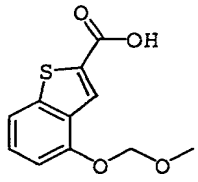

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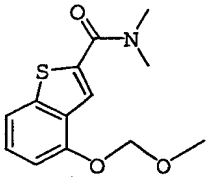

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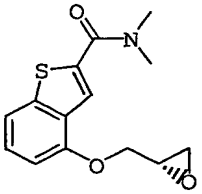

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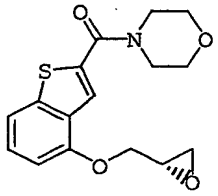

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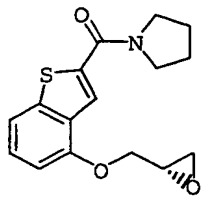

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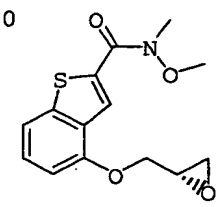

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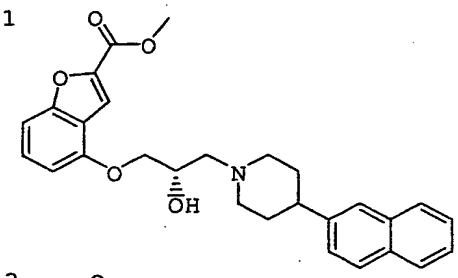

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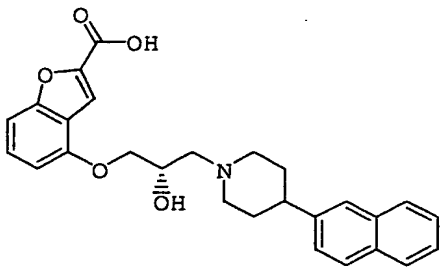

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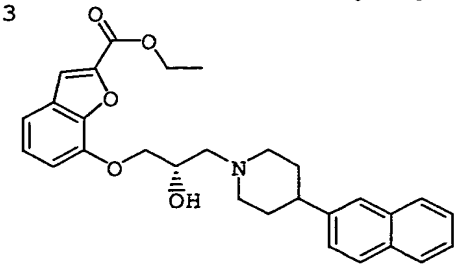

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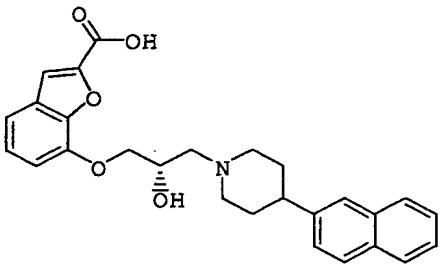

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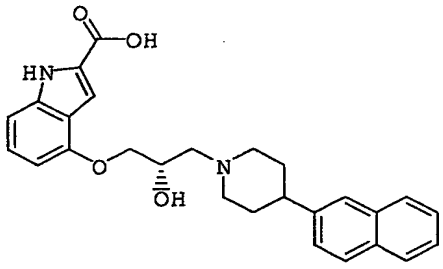

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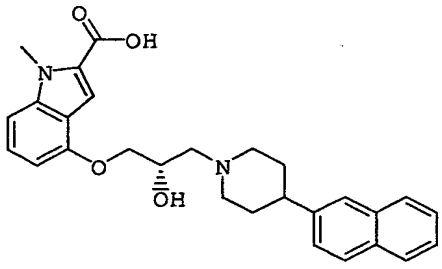

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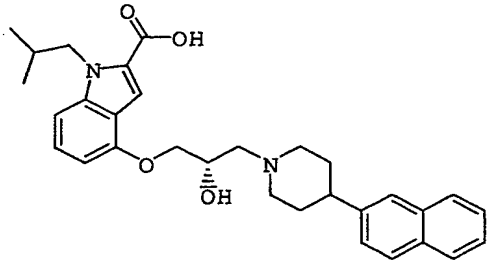

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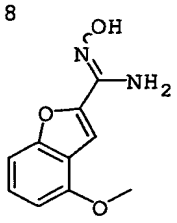

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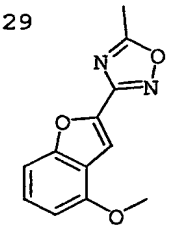

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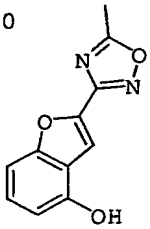

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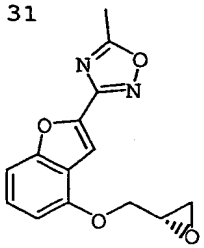

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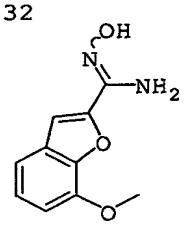

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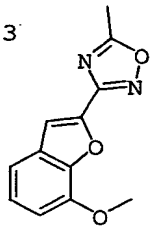

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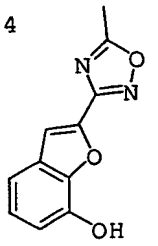

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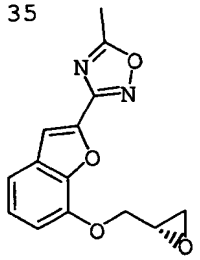

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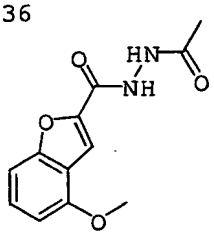

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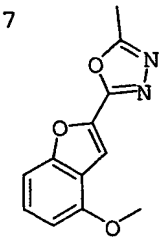

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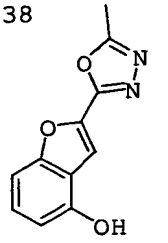

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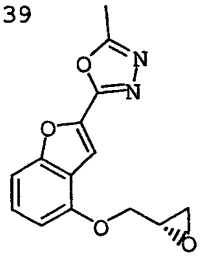

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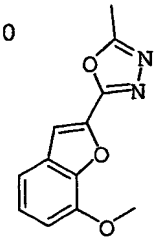

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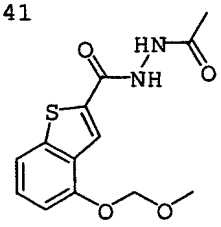

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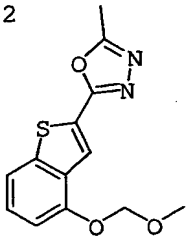

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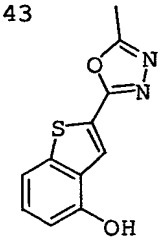

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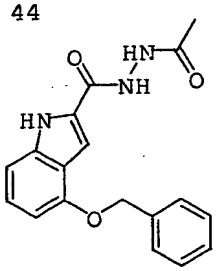

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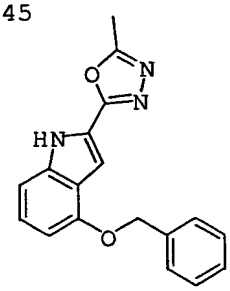

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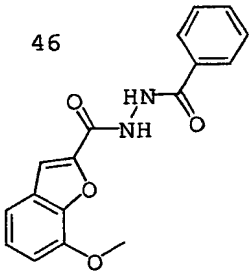

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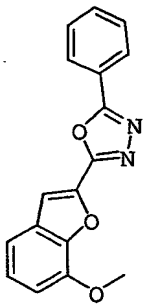

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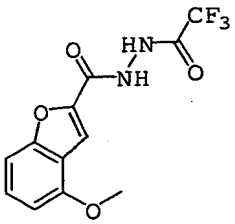

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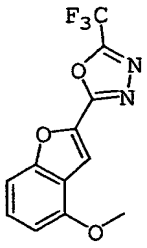

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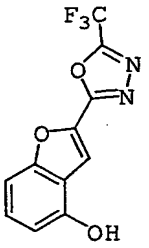

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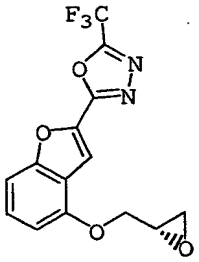

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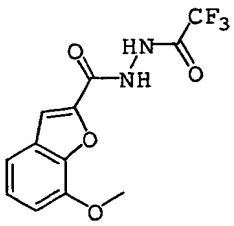

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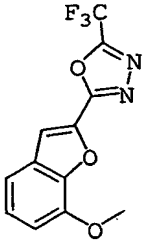

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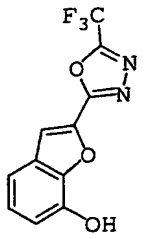

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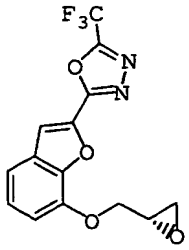

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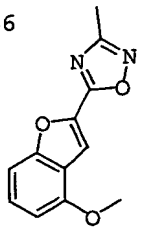

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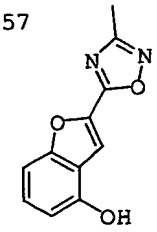

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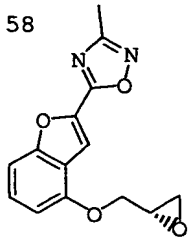

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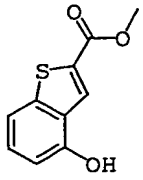

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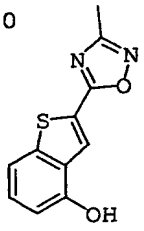

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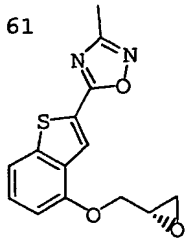

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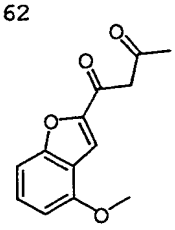

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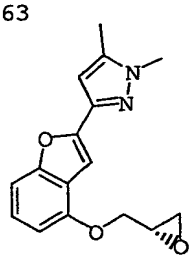

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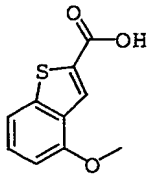

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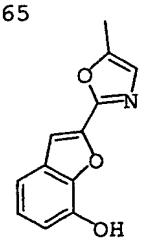

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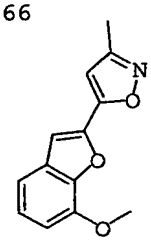

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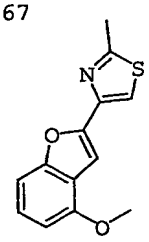

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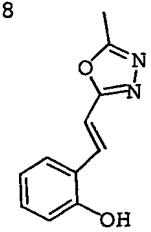

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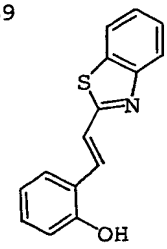

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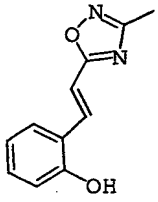

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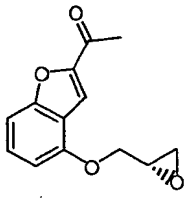

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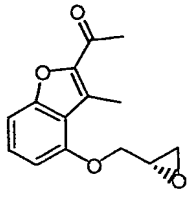

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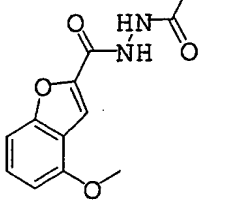

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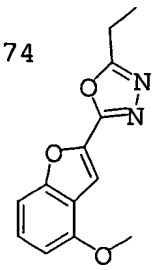

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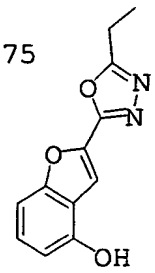

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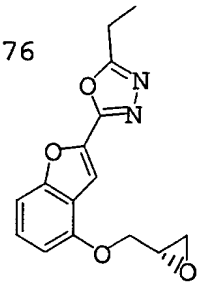

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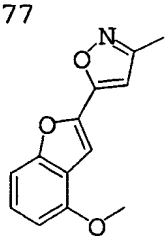

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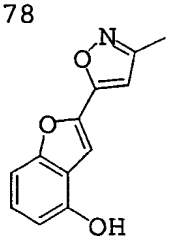

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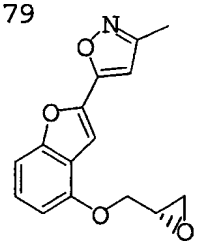

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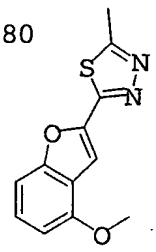

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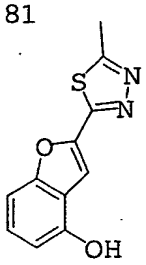

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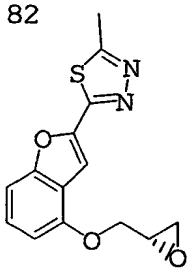

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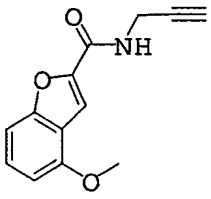

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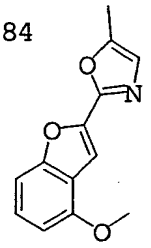

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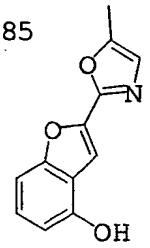

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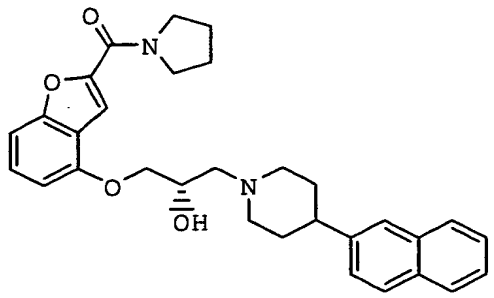
Example 1

(S)-1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylcarbonyl)pyrrolidine

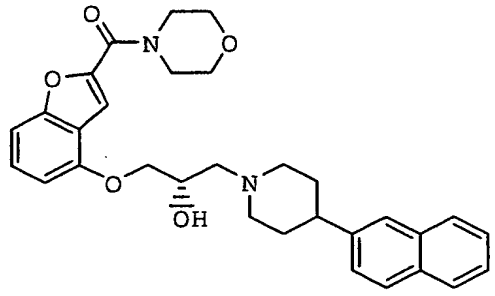


(S)-1-(4-Glycidyloxybenzo(b)furan-2-ylcarbonyl)-pyrrolidine (1.2 g) obtained in Starting Material Synthesis Example 1 was dissolved in methanol (40 ml) and 4-(naphthalen-2-yl)piperidine (0.85 g) was added. The mixture was refluxed under heating for 8 hr. The reaction mixture was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (chloroform/methanol) to give the title compound (1.6 g) as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.81-2.20(m, 8H), 2.22(t, J=11.7, 1H), 2.56-2.96(m, 1H), 2.62-2.79(m, 3H), 3.03(d, J=10.8, 1H), 3.22(d, J=10.8, 1H), 4.10-4.28(m, 3H), 6.73(d, J=8.3, 1H), 7.16(d, J=8.3, 1H), 7.33(t, J=8.3, 1H), 7.35-7.50(m, 3H), 7.51-7.55(m, 1H), 7.67(s, 1H), 7.81(d, J=8.8,3H)

Example 2

(S)-4-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylcarbonyl)morpholine



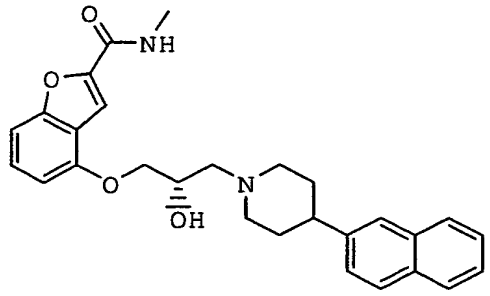
(S)-4-(4-Glycidyloxybenzo(b)furan-2-yl)morpholine (1.3 g) obtained in Starting Material Synthesis Example 2 was

dissolved in methanol (40 ml) and 4-(naphthalen-2-yl)piperidine (0.91 g) was added. The mixture was refluxed under heating for 8 hr and the reaction solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform/methanol) to give the title compound (1.8 g) as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.86-1.99(m, 4H), 2.21(t, J=11.7, 1H), 2.53(t, J=11.2, 1H), 2.59-2.74(m, 3H), 3.03(d, J=10.8, 1H), 3.22(d, J=10.8, 1H), 3.70-4.03(m, 8H), 4.10-4.27(m, 3H), 6.73(d, J=8.3, 1H), 7.15(d, J=8.3, 1H), 7.33(t, J=8.3, 1H), 7.37-7.41(m, 3H), 7.49(s, 1H), 7.67(s, 1H), 7.81(d, J=8.8,3H)

Example 3

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N-methylbenzo(b)furan-2-carboxamide

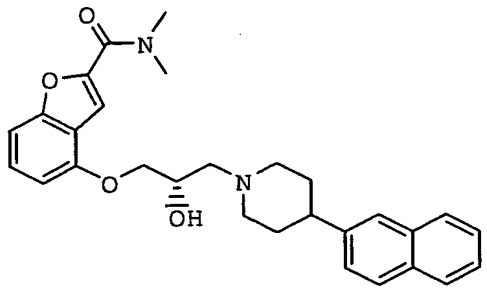


To a solution (13 ml) of (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)benzo(b)furan-2-carboxylic acid (0.12 g) obtained in Starting Material Synthesis Example 12 in DMF were added methylamine hydrochloride (0.18 g), triethylamine (0.1 ml) and diethyl cyanophosphate (0.1 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The oil layer was washed with saturated aqueous ammonium chloride solution and water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel chromatography (chloroform/methanol) to give the title compound (0.05 g) as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.84-1.97(m, 4H), 2.20(t, J=11.7, 1H), 2.45-2.55(m, 1H), 2.59-2.79(m, 3H), 2.99-3.06(m, 1H), 3.03(d, J=5.3, 3H), 3.20(d, J=9.7, 1H), 4.11-4.20(m, 3H), 6.60(br, 1H), 6.70(d, J=8.3, 1H), 7.08(d, J=8.3, 1H), 7.31(t, J=8.3, 1H), 7.35-7.41(m, 3H), 7.59(s, 1H), 7.65(s, 1H), 7.78(d, J=8.8,3H)

Example 4

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)furan-2-carboxamide

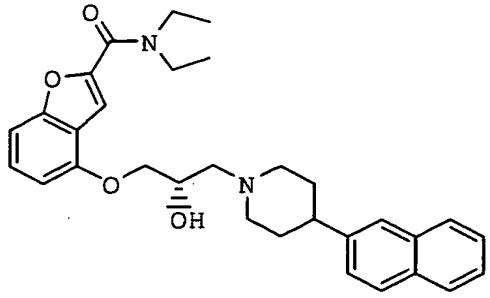


By the reactions as in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-carboxylic acid (0.8 g) obtained in Starting Material Synthesis Example 12, dimethylamine hydrochloride (0.15 g), triethylamine (0.49 ml) and diethyl cyanophosphate (0.33 ml), the title compound (0.61 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.84-2.00(m, 4H), 2.22(t, J=11.0, 1H), 2.49-2.55(m, 1H), 2.65-2.77(m, 3H), 3.03(brd, J=10.7, 1H), 3.16(brs, 3H), 3.22(brd, J=10.7, 1H), 3.36(brs, 3H), 4.14-4.24(m, 3H), 6.72(d, J=8.3, 1H), 7.16(d, J=8.3,1H), 7.31(t, J=8.3,1H), 7.39-7.48(m, 3H), 7.67(s, 1H), 7.80(d, J=8.8, 3H)

Example 5

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-diethylbenzo(b)furan-2-carboxamide

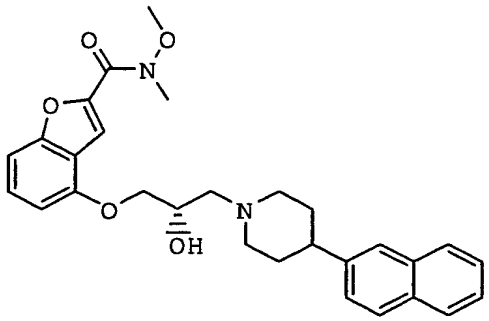


By the reactions in the same manner as in as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-carboxylic acid (0.8 g) obtained in Starting Material Synthesis Example 12, diethylamine (0.24 ml) and diethyl cyanophosphate (0.5 ml), the title compound (0.61 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.19-1.40(m, 6H), 1.82-2.00(m, 4H), 2.22(t, J=12.2, 1H), 2.49-2.55(m, 1H), 2.64-2.76(m, 3H), 3.04(brd, J=11.3, 1H), 3.21(brd, J=11.3, 1H), 3.43-3.70(m, 4H), 4.12-4.24(m, 3H), 6.72(d, J=8.3, 1H), 7.14(d, J=8.3, 1H), 7.30(t, J=8.3, 1H), 7.38-7.48(m, 3H), 7.67(s, 1H), 7.80(d, J=8.3, 3H)

Example 6

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N-methoxy-N-methylbenzo(b)furan-2-carboxamide



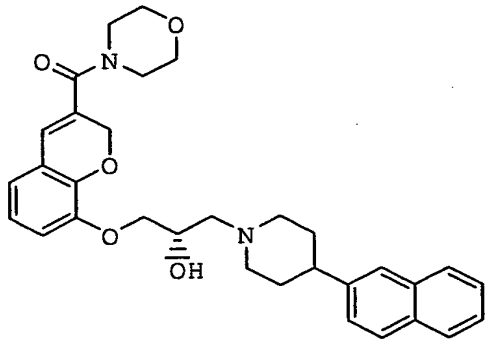
By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-carboxylic acid (0.8 g) obtained in Starting Material Synthesis Example 12, N,O-dimethylhydroxylamine hydrochloride (0.24 g), triethylamine

(1.0 ml) and diethyl cyanophosphate (0.27 ml), the title compound (0.64 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.86-1.99(m, 4H), 2.22(t, J=10.2, 1H), 2.49-2.53(m, 1H), 2.63-2.74(m, 3H), 3.04(brd, 11.7,1H), 3.22(brd, 11.7,1H), 3.42(s, 3H), 3.92(s, 3H)4.14-4.27(m, 3H), 6.72(d, J=7.8, 1H), 7.23(d, J=7.8, 1H), 7.34(t, J=7.8, 1H), 7.38-7.48(m, 3H), 7.63(s, 1H), 7.67(s, 1H), 7.79-7.82(m, 3H)

Example 7

(S)-4-(8-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-2H-chromen-3-ylcarbonyl)morpholine

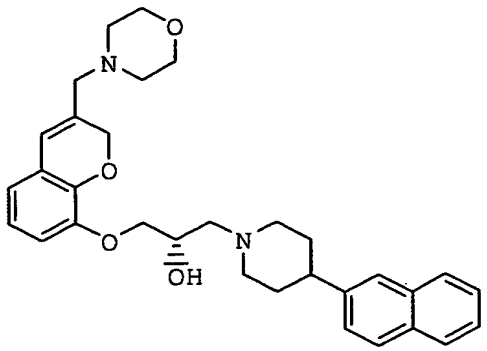


By the reactions in the same manner as in Example 1 using (S)-4-(8-glycidyloxy-2H-chromen-3-yl)morpholine (3.1 g) obtained in Starting Material Synthesis Example 6 and 4-(naphthalen-2-yl)piperidine (2.5 g), the title compound (3.5 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.86-1.99(m, 4H), 2.21(t, J=11.7, 1H), 2.49-2.56(m, 1H), 2.63-2.74(m, 3H), 3.03(d, J=11.7, 1H), 3.22(d, J=11.7, 1H), 3.42(s, 3H), 3.84(s, 3H), 4.14-4.27(m, 3H), 6.72(d, J=8.3, 1H), 7.23(d, J=8.3, 1H), 7.43(d, J=8.3, 1H), 7.44-7.48(m, 2H), 7.63(s, 1H), 7.68(s, 1H), 7.78-7.82(m, 3H)

Example 8

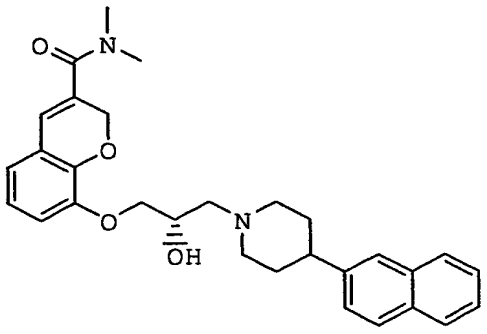
(S)-4-(8-(2-hydroxy-(3-(4-naphthalen-2-yl)piperidino)-propyloxy)-2H-chromen-3-ylmethyl)morpholine maleate



To a suspension of lithium aluminum hydride (0.55 g) in THF was added aluminum chloride (0.63 g) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was made to become 4°C and a solution of (S)-4-(8-(2-hydroxy-(3-(4-naphthalen-2-yl)piperidino)propyloxy)-2H-chromen-3-ylcarbonyl)morpholine (2.5 g) in THF (50 ml) was added dropwise. The mixture was stirred for 30 min and hydrous THF was added. The mixture was further stirred for 30 min at room temperature and the precipitated insoluble matter was filtered off through celite. The solvent was evaporated under reduced pressure to give a brown oil. This was dissolved in ethanol and maleic acid was added. The precipitated crystals were collected by filtration and dried to give the title compound (1.3 g) as pale-yellow crystals, melting point 164-166°C.

Example 9

(S)-8-(2-hydroxy-(3-(4-naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethyl-2H-chromene-3-carboxamide



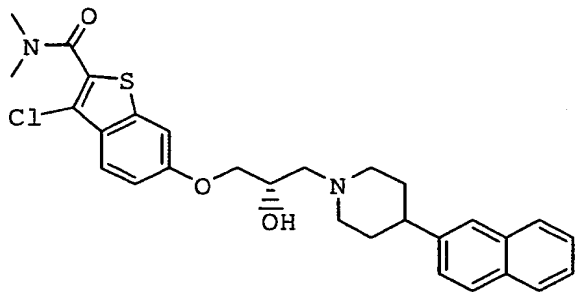
By the reactions in the same manner as in Example 1

using (S)-8-glycidyloxy-N,N-dimethyl-2H-chromene-3-carboxamide (3.2 g) obtained in Starting Material Synthesis Example 8 and 4-(naphthalen-2-yl)piperidine (1.5 g), the title compound (3.7 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.86-1.96(m, 4H), 2.19(t, J=11.7, 1H), 2.43-2.55(m, 1H), 2.59-2.89(m, 3H), 2.96(s, 3H), 2.97(s, 3H), 2.90-3.32(m, 2H), 4.07-4.32(m, 3H), 6.61(s, 1H), 6.73(d, J=8.3, 1H), 6.86(t, J=8.3, 1H), 6.93(d, J=8.3, 1H), 7.35-7.47(m, 3H), 7.66(s, 1H), 7.78-7.80(m, 3H)

Example 10

(S)-3-chloro-6-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide

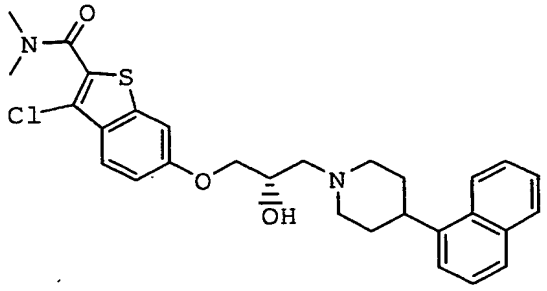


By the reactions in the same manner as in Example 1, the title compound (0.4 g) was obtained from 3-chloro-6-glycidyloxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide (0.6 g) obtained in Starting Material Synthesis Example 14 and 4-(naphthalen-2-yl)piperidine (0.45 g).

^{1}H-NMR($CDCl_3$)δ: 1.87-1.96(m, 3H), 2.05-2.22(m, 1H), 2.52-2.70(m, 4H), 3.03-3.22(m, 10H), 4.08-4.20(m, 3H), 7.13-7.16(m, 1H), 7.30(d, 1H, J=1.9), 7.39(d, 1H, J=8.8), 7.43-7.48(m, 2H), 7.60(s, 1H), 7.72(d, 1H, J=8.3), 7.77-7.82(m, 3H, J=8.3)

Example 11

(S)-3-chloro-6-(2-hydroxy-3-(4-(naphthalen-1-yl)piperidino)-propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide

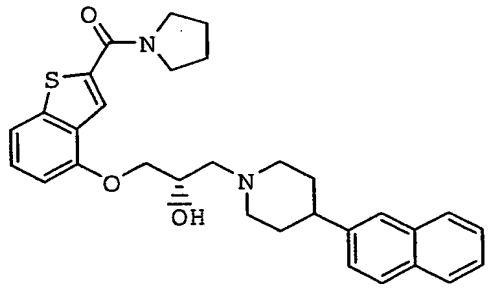


By the reactions in the same manner as in Example 1 using 3-chloro-6-glycidyloxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide (0.6 g) obtained in Starting Material Synthesis Example 14 and 4-(naphthalene-1-yl)piperidine (0.45 g), the title compound (0.5 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.81-2.33(m, 3H), 2.30-2.37(m, 1H), 2.62-2.70(m, 4H), 3.11-3.17(m, 8H), 3.21-3.25(m, 1H), 3.35-3.44(m, 1H), 4.02-4.15(m, 2H), 4.18-4.22(m, 1H), 7.15(d, 1H, J=6.8), 7.30(s, 1H), 7.40-7.49(m, 4H), 7.75-7.79(m, 2H), 7.88(d, 1H, J=7.8), 8.10(d, 1H, J=8.3)

Example 12

(S)-1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)thiophen-2-ylcarbonyl)pyrrolidine 2 methanesulfonate monohydrate

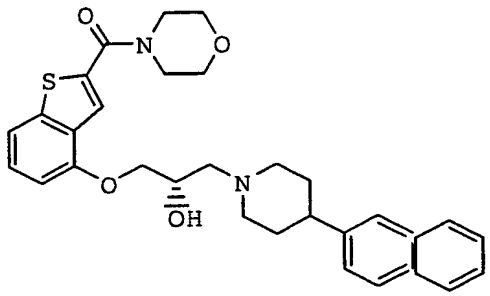


By the reactions in the same manner as in Example 1 using 1-(4-glycidyloxybenzo(b)thiophen-2-carbonyl)pyrrolidine (4.0 g) obtained in Starting Material Synthesis Example 19 and 4-(naphthalen-2-yl)piperidine (2.2 g), a brown oil (4.2 g) was obtained. This was dissolved in ethyl acetate and methanesulfonic acid was added. The precipitated crystals were

collected by filtration and dried to give the title compound (3.3 g) as pale-yellow crystals, melting point 88-90°C.

Example 13

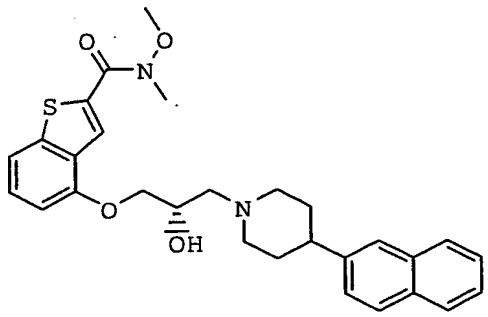
(S)-4-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)thiophen-2-ylcarbonyl)morpholine



By the reactions in the same manner as in Example 1, the title compound (0.7 g) was obtained from (S)-4-(4-glycidyloxybenzo(b)thiophen-2-ylcarbonyl)morpholine (1.2 g) obtained in Starting Material Synthesis Example 18 and 4-(naphthalen-2-yl)piperidine (1.0 g), melting point 82-86°C.

Example 14

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N-methoxy-N-methylbenzo(b)thiophen-2-ylcarboxamide

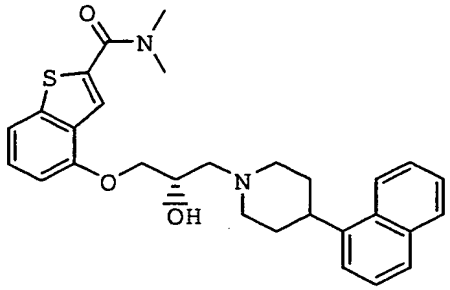


By the reactions in the same manner as in Example 1, the title compound (0.8 g) was obtained as a brown oil from 4-glycidyloxy-N-methoxy-N-methylbenzo(b)thiophene-2-ylcarboxamide (1.1 g) obtained in Starting Material Synthesis Example 20 and 4-(naphthalen-2-yl)piperidine (0.8 g).

^{1}H-NMR($CDCl_3$)δ: 1.86-1.99(m, 4H), 2.23(t, 1H, J=9.8), 2.47-2.55(m, 1H), 2.63-2.74(m, 3H), 3.05(d, 1H, J=11.2), 3.23(d, 1H, J=11.2), 3.43(s, 3H), 3.83(s, 3H), 4.11-4.15(m, 1H), 4.20-4.27(m, 2H), 6.79(d, 1H, J=7.8), 7.35-7.48(m, 5H), 7.68(s, 1H), 7.81(d, 3H, J=8.3), 8.42(s, 1H)

Example 15

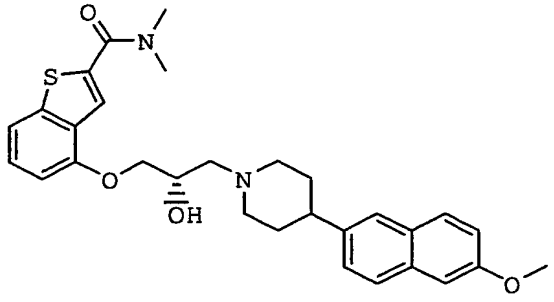
(S)-4-(2-hydroxy-3-(4-(naphthalen-1-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide



By the reactions in the same manner as in Example 1, the title compound (0.4 g) was obtained from (S)-4-glycidyloxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide (0.5 g) obtained in Starting Material Synthesis Example 17 and 4-(naphthalen-1-yl)piperidine (0.4 g), as pale-yellow crystals, melting point 97-100°C.

Example 16

(S)-4-(2-hydroxy-3-(4-(6-methoxynaphthalen-2-yl)piperidino)-propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide



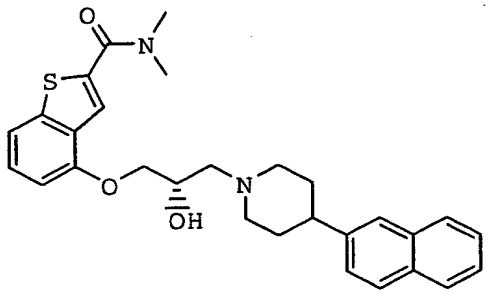
By the reactions in the same manner as in Example 1, the title compound (1.2 g) was obtained from (S)-4-glycidyloxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide (1.7 g) obtained in

Starting Material Synthesis Example 17 and 4-(6-methoxynaphthalen-2-yl)piperidine (1.5 g).

^{1}H-NMR($CDCl_3$)δ: 1.82-2.00(m, 3H), 2.07-2.23(m, 1H), 2.52-2.57(m, 1H), 2.63-2.75(m, 3H), 3.02-3.05(m, 1H), 1.10-3.20(bs, 6H), 3.91(s, 3H), 4.09-4.23(m, 3H), 6.79(d, 1H, J=7.9), 7.11(s, 1H), 7.14(d, 1H, J=2.5), 7.30-7.37(m, 2H), 7.44(d, 1H, J=7.8), 7.59(s, 1H), 7.69(s, 1H), 7.70(s, 1H), 7.74(s, 1H)

Example 17

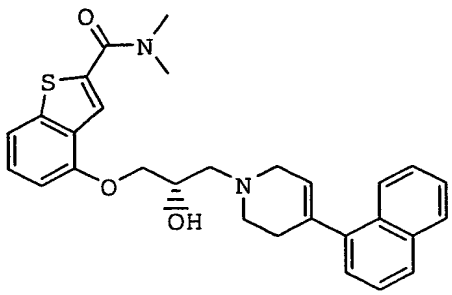
(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide (L)-tartrate



By the reactions in the same manner as in Example 1, a brown oil (1.9 g) was obtained from (S)-4-glycidyloxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide (1.2 g) obtained in Starting Material Synthesis Example 17 and 4-(naphthalen-2-yl)piperidine (0.9 g). This was dissolved in ethanol and (L)-tartaric acid was added. The precipitated crystals were collected by filtration and dried to give the title compound (1.2 g) as white crystals, melting point 173-175°C.

Example 18

(S)-4-(2-hydroxy-3-(4-(naphthalen-1-yl)-3,6-dihydro-2H-pyridin-1-yl)propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide

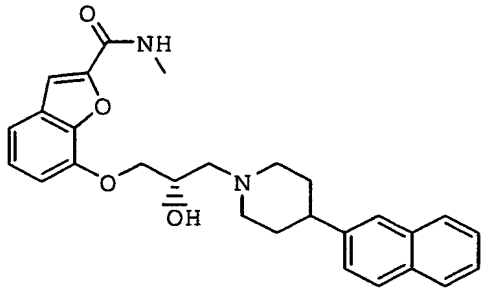


By the reactions in the same manner as in Example 1 using (S)-4-glycidyloxy-N,N-dimethylbenzo(b)thiophene-2-carboxamide (2.0 g) obtained in Starting Material Synthesis Example 17 and 4-(naphthalen-2-yl)-3,6-dihydro-2H-pyridine (2.0 g), the title compound (0.8 g) was obtained.

^{1}H-NMR($CDCl_3$)δ: 2.63-2.81(m, 6H), 3.05-3.40(m, 6H), 2.98-3.02(m, 1H), 3.41-3.44(m, 1H), 4.17-4.23(m, 2H), 4.25-4.33(m, 1H), 6.25(s, 1H), 6.79(d, 1H, J=7.9), 7.32(t, 1H, J=7.9), 7.40-7.58(m, 2H), 7.60(d, 1H, J=10.2), 7.74-7.83(m, 6H)

Example 19

(S)-7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N-methylbenzo(b)furan-2-carboxamide



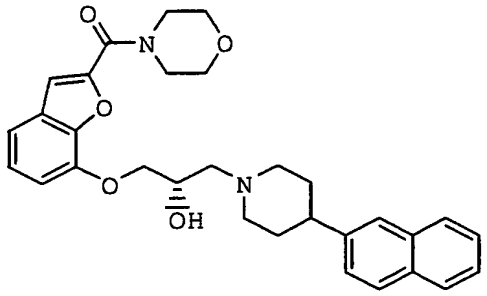
By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)benzo(b)furan-2-carboxylic acid (1.0 g) obtained in Starting Material Synthesis Example 24, methylamine (0.15 g), triethylamine (0.63 ml) and diethyl cyanophosphate (0.37 ml), the title compound (0.75 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.85-1.97(m, 4H), 2.20(t, J=11.7, 1H), 2.45-2.55(m, 1H), 2.59-2.79(m, 3H), 2.99-3.06(m, 1H), 3.04(d, J=5.3, 3H), 3.20(d, J=9.7, 1H), 4.07-4.27(m, 3H), 4.18-4.38(s, m), 6.82(br, 1H), 6.94(d, J=8.3, 1H), 7.18(t, J=8.3, 1H), 7.31(t, J=8.3, 1H), 7.37-7.46(m, 3H), 7.66(s, 1H), 7.79(d, J=8.8, 3H)

Example 20

(S)-4-(7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-

propyloxy)benzo(b)furan-2-ylcarbonyl)morpholine

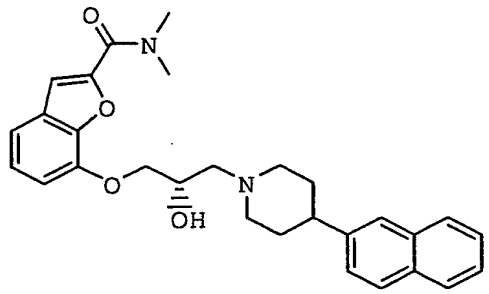


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-carboxylic acid (1.0 g) obtained in Starting Material Synthesis Example 24, morpholine (0.19 g), triethylamine (0.63 ml) and diethyl cyanophosphate (0.37 ml), the title compound (0.60 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.86-1.99(m, 4H), 2.22(t, J=11.7, 1H), 2.53-2.58(m, 1H), 2.59-2.80(m, 3H), 3.03(d, J=10.8, 1H), 3.23(d, J=10.8, 1H), 3.72-4.03(m, 8H), 4.20-4.36(m, 3H), 6.96(d, J=8.3, 1H), 7.22(t, J=8.3, 1H), 7.25(d, J=8.3, 1H), 7.37-7.41(m, 3H), 7.49(s, 1H), 7.66(s, 1H), 7.81(d, J=8.8, 3H)

Example 21

(S)-7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)furan-2-carboxamide



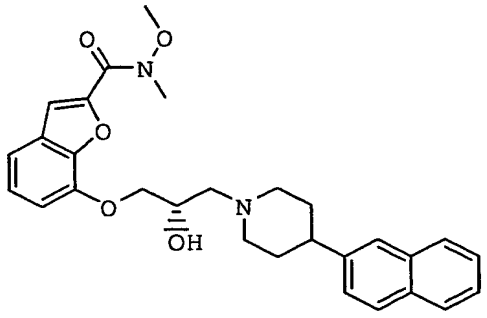
By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-carboxylic acid (1.0 g) obtained in Starting Material Synthesis Example 24, dimethylamine hydrochloride (0.18 g), triethylamine (0.63 ml) and diethyl

cyanophosphate (0.37 ml), the title compound (0.60 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.81-2.01(m, 4H), 2.18-2.29(m, 1H), 2.44-2.58(m, 1H), 2.61-2.78(m, 3H), 2.88(s, 3H), 2.95(s, 3H), 3.03(d, J=10.8, 1H), 3.24(d, J=10.8, 1H), 4.20-4.37(m, 3H), 6.95(d, J=7.8, 1H), 7.19(t, J=7.8, 1H), 7.25(d, J=7.8, 1H), 7.31(s, 1H), 7.38-7.48(m, 3H), 7.66(s, 1H), 7.80(d, J=8.8, 3H)

Example 22

(S)-7-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N-methoxy-N-methylbenzo(b)furan-2-carboxamide

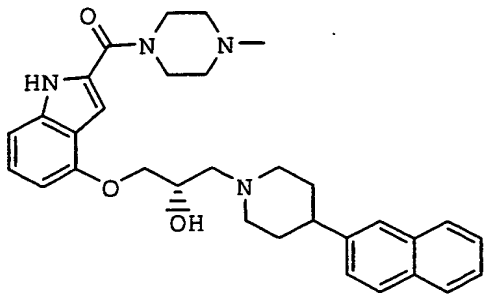


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)benzo(b)furan-2-carboxylic acid (1.0 g) obtained in Starting Material Synthesis Example 24, N,O-dimethylhydroxylamine (0.21 g), triethylamine (0.63 ml) and diethyl cyanophosphate (0.37 ml), the title compound (0.62 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.83-2.01(m, 4H), 2.21-2.29(m, 1H), 2.43-2.58(m, 1H), 2.63-2.78(m, 3H), 3.03(brd, J=10.8, 1H), 3.23(d, J=10.8, 1H), 3.42(s, 3H), 3.86(s, 3H), 4.21-4.38(m, 3H), 6.98(d, J=7.8, 1H), 7.20(t, J=7.8, 1H), 7.38-7.48(m, 3H), 7.66(s, 1H), 7.80(d, J=8.8, 3H)

Example 23

(S)-1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1H-indol-2-ylcarbonyl)-4-methylpiperazine

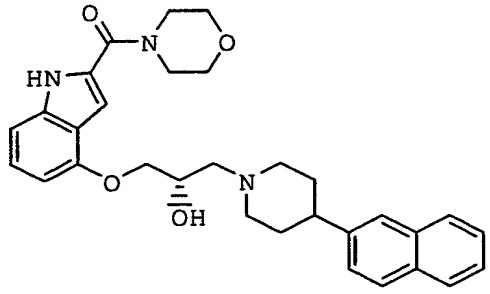


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1H-indole-2-carboxylic acid (0.70 g) obtained in Starting Material Synthesis Example 25, N-methylpiperazine (0.16 g), triethylamine (0.44 ml) and diethyl cyanophosphate (0.27 ml), the title compound (0.65 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.73-2.04(m, 4H), 2.16-2.20(m, 1H), 2.34(s, 3H), 2.49-2.79(m, 7H), 3.03(d, J=10.7, 1H), 3.15-3.36(m, 5H), 4.10-4.37(m, 3H), 6.54(d, J=8.3, 1H), 6.93(s, 1H), 7.00(d, J=8.3, 1H), 7.18(t, J=8.3, 1H), 7.38-7.46(m, 3H), 7.67(s, 1H), 7.78(m, 3H), 9.29(s, 1H)

Example 24

(S)-4-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1H-indol-2-ylcarbonyl)morpholine hydrochloride

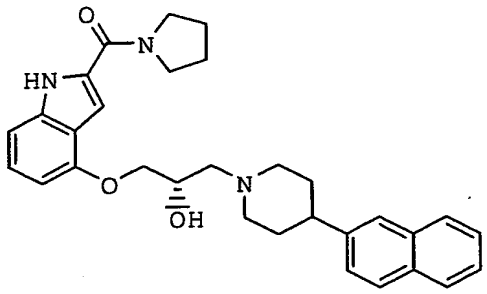


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-naphthalen-2-yl)piperidino)-propyloxy)-1H-indole-2-carboxylic acid (0.70 g) obtained in Starting Material Synthesis Example 25, morpholine (0.14 g), triethylamine (0.44 ml) and diethyl cyanophosphate (0.27 ml), a

brown oil (0.66 g) was obtained. This was dissolved in acetone and 1N solution of hydrochloric acid in methanol was added. The precipitated crystals were collected by filtration and dried to give the title compound (0.65 g) as white crystals, melting point 169-171°C.

Example 25

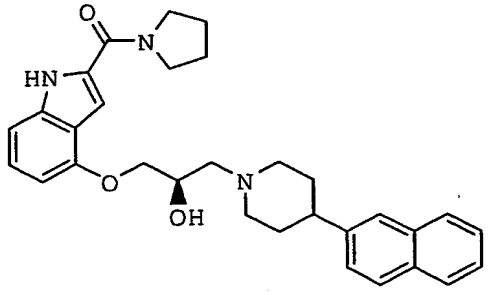
(S)-1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1H-indol-2-ylcarbonyl)pyrrolidine 3/2 hydrochloride



By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-naphthalen-2-yl)piperidino)-propyloxy)-1H-indole-2-carboxylic acid (0.70 g) obtained in Starting Material Synthesis Example 25, pyrrolidine (0.11 g), triethylamine (0.44 ml) and diethyl cyanophosphate (0.27 ml), the title compound (0.24 g) was obtained as white crystals, melting point 158-161°C.

Example 26

(R)-1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1H-indol-2-ylcarbonyl)pyrrolidine

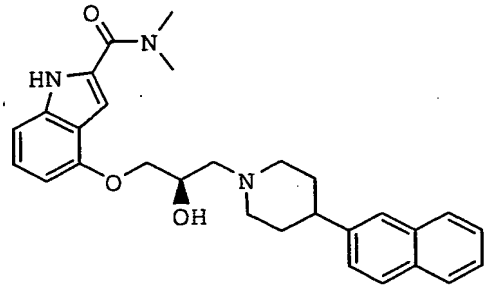


By the reactions in the same manner as in Example 3 using (R)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-

propyloxy)-1H-indole-2-carboxylic acid (1.0 g) obtained by the reactions in the same manner as in Starting Material Synthesis Example 25 from (R)-glycidyl nosylate, pyrrolidine (0.30 g), triethylamine (3.0 ml) and diethyl cyanophosphate (0.30 ml), the title compound (0.54 g) was obtained as white crystals, melting point 211-212°C.

Example 27

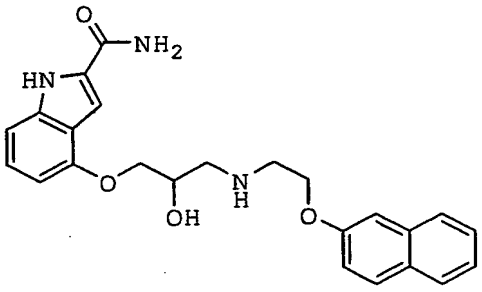
(R)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethyl-1H-indole-2-carboxamide



By the reactions in the same manner as in Example 3 using (R)-4-(2-hydroxy-3-(4-naphthalen-2-yl)piperidino)propyloxy)-1H-indole-2-carboxylic acid (1.0 g) obtained by the reactions in the same manner as in Starting Material Synthesis Example 25 from (R)-glycidyl nosylate, dimethylamine hydrochloride (0.3 g), triethylamine (3.0 ml) and diethyl cyanophosphate (0.3 ml), the title compound (0.24 g) was obtained as white crystals, melting point 158-160°C.

Example 28

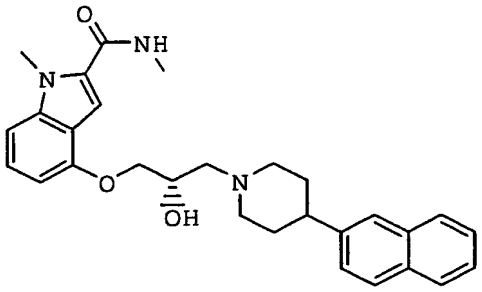
4-(2-hydroxy-3-(2-(2-naphthoxy)ethylamino)propyloxy)-1H-indole-2-carboxamide



By the reactions in the same manner as in Example 1 using 4-glycidyloxy-1H-indole-carboxamide (0.70 g) and 2-(2-naphthoxy)ethylamine (0.70 g), the title compound (0.57 g) was obtained as white crystals, melting point 125-126°C.

Example 29

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-methyl-N-methy-lindole-2-carboxamide

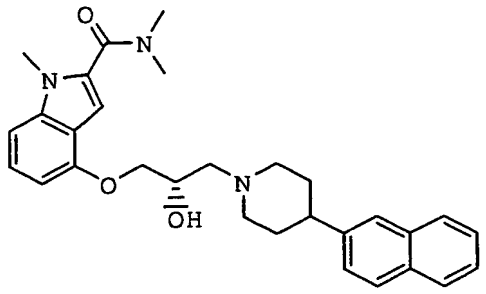


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-methylindole-2-carboxylic acid (1.0 g) obtained in Starting Material Synthesis Example 26, methylamine hydrochloride (0.2 g), triethylamine (1.0 ml) and diethyl cyanophosphate (0.5 ml), a yellow oil (0.8 g) was obtained. To this oil was added isopropyl ether and the precipitated crystals were collected by filtration to give the title compound (0.5 g) as pale-yellow crystals, melting point 180-183°C.

^{1}H-NMR($CDCl_3$)δ: 1.87-1.96(m, 4H), 2.19-2.50(m, 1H), 2.50-2.80(m, 4H), 2.90-3.20(m, 4H), 3.21(m, 1H), 4.04(s, 3H), 4.14-4.18(m, 3H), 6.19(brs, 1H),6.55(d, J=7.8, 1H), 6.98-7.08(m, 2H), 7.20-7.22(m, 1H), 7.38-7.46(m, 3H), 7.66(m, 1H), 7.79-7.81(m, 3H)

Example 30

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-methyl-N,N-dimethyl-indole-2-carboxamide

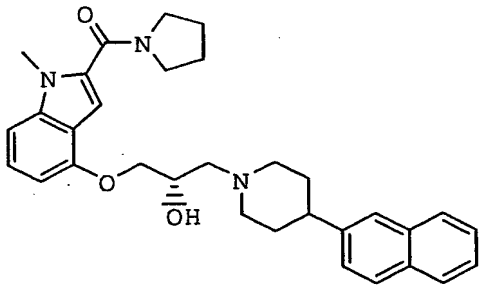


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-methyl-indole-2-carboxylic acid (0.6 g) obtained in Starting Material Synthesis Example 26, dimethylamine hydrochloride (0.3 g), triethylamine (1.0 ml) and diethyl cyanophosphate (0.5 ml), the title compound (0.6 g) was obtained as pale-yellow crystals, melting point 146-148°C.

^{1}H-NMR($CDCl_3$)δ: 1.84-1.93(m, 4H), 2.16-2.20(m, 1H), 2.50-2.80(m, 4H), 3.00-3.40(m, 8H), 3.81(s, 3H), 4.10-4.30(m, 3H), 6.54(d, J=8.4, 1H), 6.77(s, 1H), 6.96(d, J=8.3, 1H), 7.18(dd, J=7.8, 7.8, 1H), 7.24(s, 1H), 7.36-7.45(m, 3H), 7.64(s, 1H), 7.78(d,J=7.8, 2H)

Example 31

(S)-1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-methyl-indole-2-carbonyl)pyrrolidine

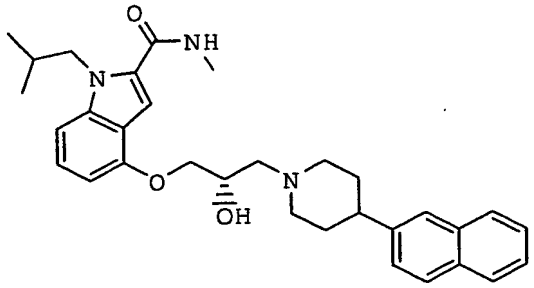


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-methyl-indole-2-carboxylic acid (1.8 g) obtained in Starting Material Synthesis Example 26, pyrrolidine (0.5 ml), triethylamine (0.5 ml) and diethyl cyanophosphate (1.5 ml), the

title compound (0.2 g) was obtained as a yellow oil.
^{1}H-NMR($CDCl_3$)δ: 1.84-2.04(m, 9H), 2.23(m, 1H), 2.50(m, 1H), 2.66-2.80(m, 2H), 3.00-3.30(m, 2H), 3.60-3.80(m, 4H), 3.92(s, 3H), 4.00-4.30(m, 3H), 6.55(d, J=7.8, 1H), 6.89(s, 1H), 6.99(d, J=8.3, 1H), 7.22(dd, J=7.8, 8.3, 1H), 7.38(s, 1H), 7.40-7.47(m, 3H), 7.66(s, 1H), 7.80(d, J=7.3, 2H)

Example 32

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-(2-methylpropyl)-indole-2-carboxylic acid N-methylamide hydrochloride 1/2 hydrate

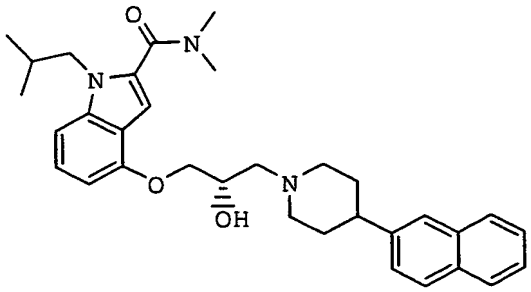


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-(2-methylpropyl)indole-2-carboxylic acid (1.0 g) obtained in Starting Material Synthesis Example 27, methylamine hydrochloride (0.2 g), triethylamine (0.7 ml) and diethyl cyanophosphate (0.5 ml), a yellow oil (0.8 g) was obtained. A 1N solution of hydrochloric acid in isopropyl was added to this oil in isopropyl ether. The precipitated crystals were collected by filtration and dried to give the title compound (0.7 g) as pale-yellow crystals, melting point 108-110°C.
^{1}H-NMR(CD_3OD)δ: 1.10-1.12(m, 7H), 2.09-2.24(m, 5H), 2.91(s, 3H), 3.11-3.60(m, 4H), 3.84-3.92(m, 2H), 4.15-4.25(m, 2H), 4.37(d, J=7.4, 2H), 4.57(m, 1H), 6.60(d, J=7.8, 1H), 7.09(d, J=8.3, 1H), 7.16-7.22(m, 2H), 7.43-7.46(m, 3H), 7.74-7.867(m, 4H)

Example 33

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-(2-methylpropyl)-indole-2-carboxylic acid N,N-dimethylamide

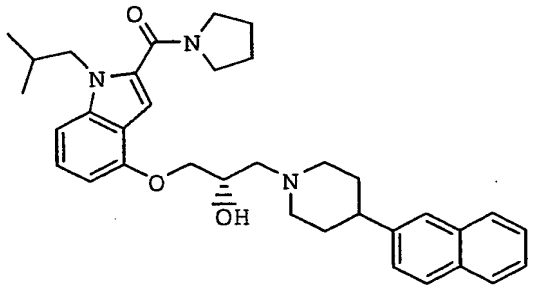
hydrochloride 1/2 hydrate



By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-(2-methylpropyl)indole-2-carboxylic acid (1.0 g) obtained in Starting Material Synthesis Example 27, dimethylamine hydrochloride (0.2 g), triethylamine (0.7 ml) and diethyl cyanophosphate (0.5 ml), the title compound (0.6 g) was obtained as pale-yellow crystals, melting point 108-110°C.
^{1}H-NMR(CD_3OD)δ: 1.10-1.12(m, 7H), 2.03(m, 1H), 2.10-2.30(m, 4H), 3.00-3.40(m, 8H), 3.40-3.60(m, 2H), 3.80-3.95(m, 2H), 4.12(d, J=7.8, 2H), 4.20-4.25(m, 2H), 4.57(m, 1H), 6.62(d, J=7.8, 1H), 6.87(s, 1H), 7.10(d, J=8.3, 1H), 7.17(dd, J=7.8, 8.3m, 1H), 7.43-7.49(m, 3H), 7.74-7.86(m, 4H)

Example 34

(S)-1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-(2-methylpropyl)-indole-2-carbonyl)pyrrolidine hydrochloride



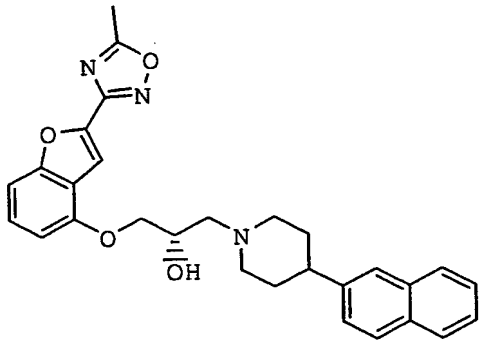
By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-(2-methylpropyl)-indole-2-carboxylic acid (1.0 g)

obtained in Starting Material Synthesis Example 27, pyrrolidine (0.2 ml), triethylamine (0.7 ml) and diethyl cyanophosphate (0.5 ml), the title compound (0.4 g) was obtained as pale-yellow crystals, melting point 104-106°C.

^{1}H-NMR(CD_3OD)δ: 0.79-0.81(m, 7H), 1.91-2.14(m, 9H), 3.00-3.40(m, 4H), 3.60-3.80(m, 6H), 4.15-4.25(m, 4H), 4.57(m, 1H), 6.61(d, J=7.8, 1H), 6.98(s, 1H), 7.08(d, J=8.3, 1H), 7.20(dd, J=7.8, 8.3m, 1H), 7.42-7.69(m, 3H), 7.72-7.84(m, 4H)

Example 35

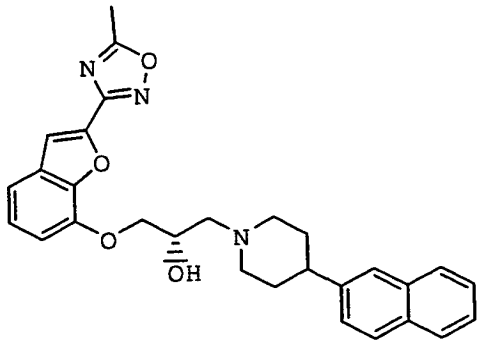
(S)-1-(2-(5-methyl-1,2,4-oxadiazol-3-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol



By the reactions in the same manner as in Example 3 using (S)-3-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole (0.45 g) obtained in Starting Material Synthesis Example 31 and 4-(naphthalen-2-yl)piperidine (0.35 g), the title compound (0.65 g) was obtained as white crystals, melting point 146-148°C.

Example 36

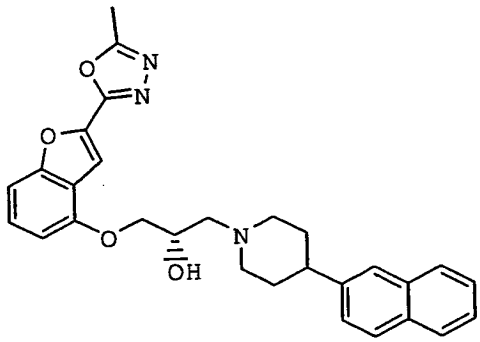
(S)-1-(2-(5-methyl-1,2,4-oxadiazol-3-yl)benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol



By the reactions in the same manner as in Example 1 using (S)-3-(7-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,2,4-oxadiazole (1.7 g) obtained in Starting Material Synthesis Example 35 and 4-(naphthalen-2-yl)piperidine (1.3 g), the title compound (2.0 g) was obtained as white crystals, melting point 169-170°C.

Example 37

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol hydrochloride

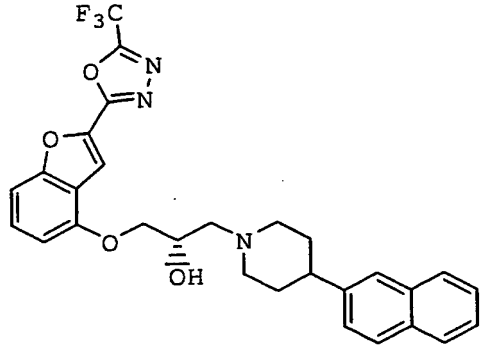


By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole (0.33 g) obtained in Starting Material Synthesis Example 39 and 4-(naphthalen-2-yl)piperidine (0.26 g), a brown oil (0.5 g) was obtained. This was dissolved in ethyl acetate and 1N solution of hydrochloric acid in ether was added. The precipitated crystals were collected by filtration and dried to give the title compound (0.30 g) as pale-yellow crystals,

melting point 158-160°C.

Example 38

(S)-1-(2-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

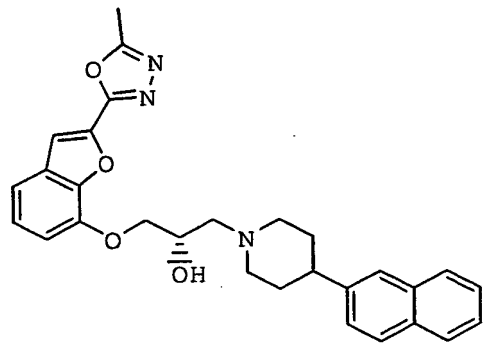


By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole (1.0 g) obtained in Starting Material Synthesis Example 51 and 4-(naphthalen-2-yl)piperidine (0.75 g), the title compound (0.5 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.87-2.00(m, 4H), 2.23(t, J=11.7, 1H), 2.51-2.58(m, 1H), 2.63-2.76(m, 3H), 3.05(brd, J=10.3, 1H), 3.23(brd, J=10.3, 1H), 4.15-4.26(m, 3H), 6.79(d, J=8.3, 1H), 7.26(d, J=8.3, 1H), 7.39-7.48(m, 4H), 7.64(s, 1H), 7.80(d, J=8.3, 4H)

Example 39

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol



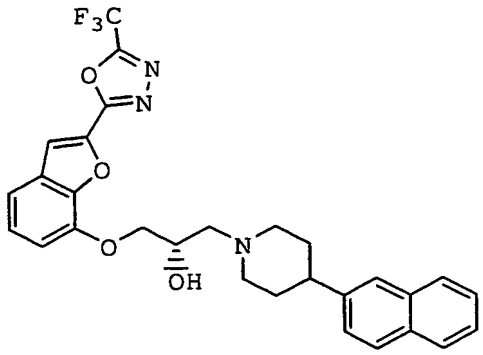
To a solution of (S)-2-(7-methoxybenzo(b)furan-2-yl)-5-

methyl-1,3,4-oxadiazole (8.0 g) obtained in Starting Material Synthesis Example 40 in methylene chloride (100 ml) was added dropwise boron tribromide (10 ml) at -8°C. The mixture was stirred under ice-cooling for 1 hr. The reaction mixture was poured into ice water and the mixture was extracted with chloroform. The oil layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give red crystals (6.0 g) of 7-hydroxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan. This compound and (S)-glycidyl nosylate (7.25 g) were dissolved in dimethylformamide (100 ml) and potassium carbonate (11 g) was added. The mixture was heated at 50°C for 2 hr. The reaction mixture was poured into ice water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily product (6.0 g). The oily product and 4-(naphthalen-2-yl)piperidine were dissolved in methanol (50 ml) and the mixture was refluxed under heating for 1 hr. After cooling, the solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (3.0 g) as pale-yellow crystals, melting point 140-142°C.

^{1}H-NMR(DMSO-d_6)δ: 1.77-1.83(m, 4H), 2.20-2.25(m, 2H), 2.47-2.66(m, 3H), 2.62(s, 3H), 3.04-3.13(m, 2H), 4.17(m, 2H), 4.30(m, 1H), 5.02(bs, 1H), 7.14(d, J=7.8, 1H), 7.29(t, J=7.8, 1H), 7.34(d, J=7.8, 1H), 7.41-7.48(m, 3H), 7.70(s, 1H), 7.72(s, 1H), 7.81-7.84(m, 3H)

Example 40

(S)-1-(2-(5-trifluoromethyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

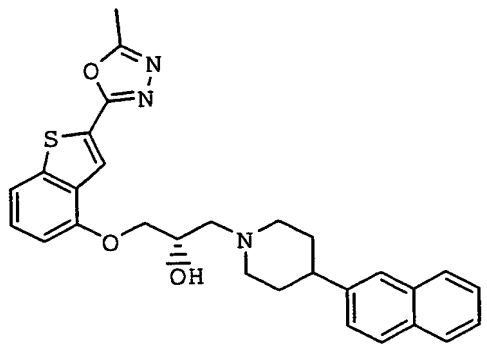


By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-trifluoromethyl-1,3,4-oxadiazole (1.0 g) obtained in Starting Material Synthesis Example 55 and 4-(naphthalen-2-yl)piperidine (0.80 g), the title compound (0.35 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.81-2.00(m, 4H), 2.21-2.25(m, 1H), 2.47-2.60(m, 1H), 2.60-2.79(m, 3H), 3.07(d, J=9.8, 1H), 3.21-3.30(m, 1H), 4.23-4.31(m, 3H), 7.02-7.09(m, 1H), 7.21-7.36(m, 3H), 7.40-7.54(m, 3H), 7.68(s, 1H), 7.81(d, J=7.8, 1H)

Example 41

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)thiophen-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol



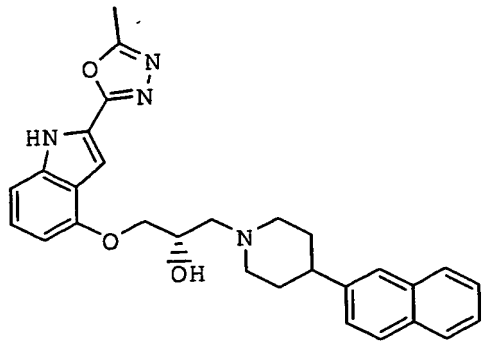
2-(4-Hydroxybenzo(b)thiophen-2-yl)-5-methyl-1,3,4-oxadiazole (1.4 g) obtained in Starting Material Synthesis Example 43 and (S)-glycidyl nosylate (1.3 g) were dissolved in dimethylformamide (15 ml) and potassium carbonate (1.5 g) was added. The mixture was heated at 50°C for 2 hr. The reaction mixture was poured into ice water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oil (1.7 g). The oil and 4-(naphthalen-2-yl)piperidine were dissolved in methanol (20 ml) and the mixture was refluxed under heating for 1 hr. After cooling, the solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (0.36 g) as a brown oil.

^{1}H-NMR(DMSO-d_6)δ: 1.77-1.85(m, 4H), 2.18-2.25(m, 2H), 2.49-2.68(m, 3H), 2.61(s, 3H), 3.05-3.15(m, 2H), 4.18(m, 2H), 4.36(m, 1H), 5.02(bs, 1H), 7.01(d, J=7.8, 1H), 7.32(t, J=7.8, 1H), 7.34(d, J=7.8, 1H), 7.41-7.48(m, 3H), 7.74(s, 1H), 7.81-7.84(m, 3H), 8.07(s, 1H)

Example 42

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indol-4-yloxy)-3-

(4-(naphthalen-2-yl)piperidino)-2-propanol



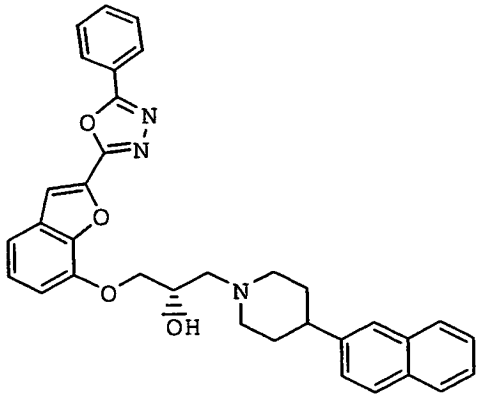
4-Benzyloxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indole (5.0 g) obtained in Starting Material Synthesis Example 45 was dissolved in a mixed solvent (500 ml) of methanol - dimethylformamide (3:2) and 5% palladium-carbon (0.5 g) was added. The mixture was stirred for 5 hr under a hydrogen flow. The catalyst was removed by filtration through celite and the filtrate was concentrated under reduced pressure. To a solution of the obtained 4-hydroxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)-indole in dimethylformamide were added (S)-glycidyl nosylate (4 g) and potassium carbonate (4.2 g), and the mixture was heated at 50°C for 5 hr. The reaction mixture was poured into ice water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol) to give yellow crystals (1 g). The yellow crystals and 4-(naphthalen-2-yl)piperidine were dissolved in methanol (10 ml) and the mixture was refluxed under heating for 2 hr. After cooling, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (0.54 g) as yellow crystals, melting point 215-217°C.

^{1}H-NMR(DMSO-d_6)δ: 1.78-1.83(m, 4H), 2.22-2.25(m, 2H), 2.51-2.63(m, 3H), 2.58(s, 3H), 3.05-3.13(m, 2H), 4.05(m, 1H), 4.16(m,

2H), 4.89(bs, 1H), 6.58(d, J=7.8, 1H), 7.04(d, J=7.8, 1H), 7.13-7.19(m, 2H), 7.42(m, 3H), 7.70(s, 1H), 7.82(m, 3H), 12.16(s, 1H)

Example 43

(S)-3-(4-(naphthalen-2-yl)piperidino)-1-(2-(5-phenyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-7-yloxy)-2-propanol



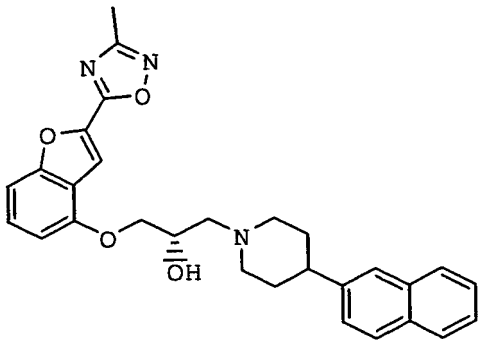
To a solution of 2-(7-methoxybenzo(b)furan-2-yl)-5-phenyl-1,3,4-oxadiazole (3.7 g), obtained in Starting Material Synthesis Example 47, in methylene chloride (100 ml) was added dropwise boron tribromide (4 ml) with stirring at -8°C. The mixture was then stirred for 1 hr under ice-cooling, and the reaction mixture was poured into ice water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give yellow crystals (2.7 g) of 7-hydroxy-2-(5-phenyl-1,3,4-oxadiazol-2-yl)benzo(b)furan. This compound and (S)-glycidyl nosylate (2.6 g) were dissolved in dimethylformamide (50 ml) and potassium carbonate (2.8 g) was added. The mixture was heated at 50°C for 2 hr. The reaction mixture was poured into ice water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily product (1.7 g). The oily product and 4-(naphthalen-2-yl)piperidine were dissolved in methanol (20 ml) and the mixture was refluxed under heating

for 1 hr. After cooling, the solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (2.3 g) as pale-yellow crystals, melting point 78-80°C.

^{1}H-NMR(DMSO-d_6)δ: 1.77-1.83(m, 4H), 2.21-2.23(m, 2H), 2.51-2.66(m, 3H), 3.05-3.14(m, 2H), 4.18(m, 2H), 4.33(m, 1H), 5.05(bs, 1H), 7.18(d, J=7.8, 1H), 7.32(t, J=7.8, 1H), 7.38-7.44(m, 4H), 7.65-7.70(m, 4H), 7.80-7.84(m, 3H), 7.90(s, 1H), 8.18(m, 2H)

Example 44

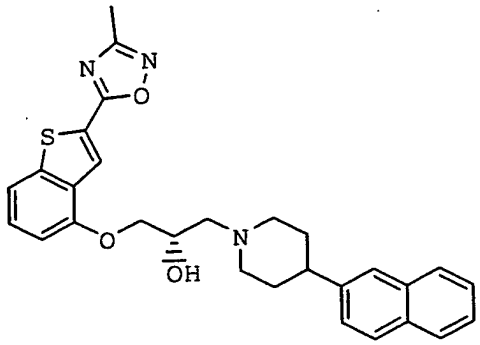
(S)-1-(2-(3-methyl-1,2,4-oxadiazol-5-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol hydrochloride



By the reactions in the same manner as in Example 1 using (S)-5-(4-glycidyloxybenzo(b)furan-2-yl)-3-methyl-1,2,4-oxadiazole (0.46 g) obtained in Starting Material Synthesis Example 58 and 4-(naphthalen-2-yl)piperidine (0.43 g), a brown oil (1.0 g) was obtained. This compound was dissolved in ethyl acetate and 1N solution of hydrochloric acid in ether was added. The precipitated crystals were collected by filtration and dried to give the title compound (0.33 g) as brown crystals, melting point 216-218°C (decomposition).

Example 45

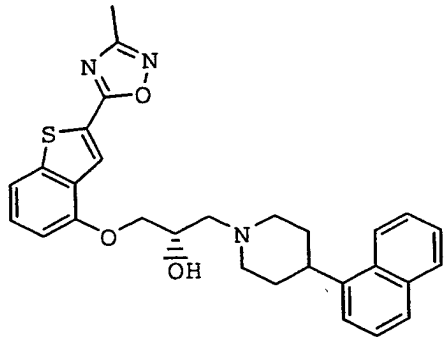
(S)-3-(4-(naphthalen-2-yl)piperidino)-1-(2-(3-methyl-1,2,4-oxadiazol-5-yl)benzo(b)thiophen-4-yloxy)-2-propanol



By the reactions in the same manner as in Example 1 using (S)-5-(4-glycidyloxybenzo(b)thiophen-2-yl)-3-methyl-1,2,4-oxadiazole (1.5 g) obtained in Starting Material Synthesis Example 61 and 4-(naphthalen-2-yl)piperidine (1.0 g), the title compound (1.5 g) was obtained as brown crystals, melting point 180-182°C.

Example 46

(S)-3-(4-(naphthalen-1-yl)piperidino)-1-(2-(3-methyl-1,2,4-oxadiazol-5-yl)benzo(b)thiophen-4-yloxy)-2-propanol hydrochloride

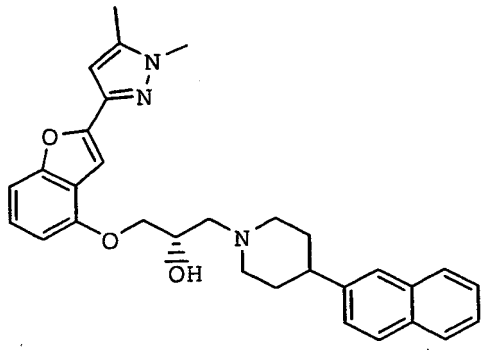


By the reactions in the same manner as in Example 1 using 5-(4-glycidyloxybenzo(b)thiophen-2-yl)-3-methyl-1,2,4-oxadiazole (0.73 g) obtained in Starting Material Synthesis Example 61 and 4-(naphthalen-1-yl)piperidine (1.0 g), a brown oil (1.5 g) was obtained as brown crystals. This compound was dissolved in ethyl acetate and 1N solution of hydrochloric acid in ether was added. The precipitated crystals were collected by filtration and dried to give the title compound (0.5 g) as

pale-yellow crystals, melting point 235°C or higher (decomposition).

Example 47

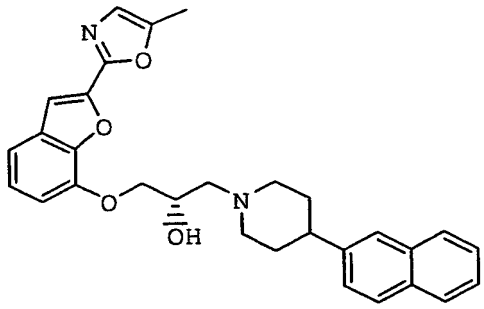
(S)-1-(2-(1,5-dimethylpyrazol-3-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol 1/4 hydrate



By the reactions in the same manner as in Example 1 using (S)-3-(4-glycidyloxybenzo(b)furan-2-yl)-1,5-dimethylpyrazole (0.2 g) obtained in Starting Material Synthesis Example 63 and 4-(naphthalen-2-yl)piperidine (0.15 g), the title compound (0.16 g) was obtained, melting point 155-157°C.

Example 48

(S)-1-(2-(5-methyloxazol-2-yl)benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

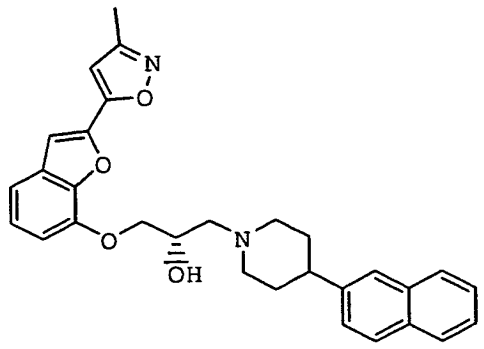


By the reactions in the same manner as in Starting Material Synthesis Example 1 using 2-(7-hydroxybenzo(b)furan-2-yl)-5-methyloxazole (2.0 g) obtained in Starting Material Synthesis Example 65 and (S)-glycidyl nosylate (1.8 g), (S)-7-

glycidyloxy-2-(5-methyloxazol-2-yl)benzo(b)furan (1.5 g) was obtained. Then, by the reactions in the same manner as in Example 1 using 4-(naphthalen-1-yl)piperidine (0.7 g), the title compound (0.26 g) was obtained, melting point 147-149°C.

Example 49

(S)-1-(2-(3-methylisoxazol-5-yl)benzo(b)furan-7-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol



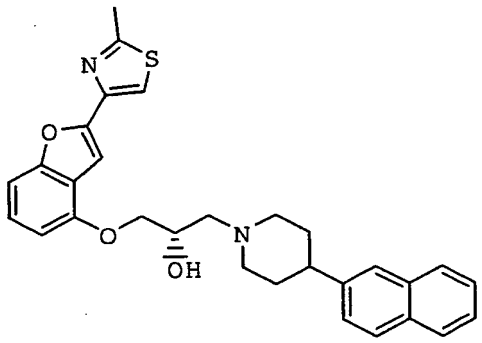
5-(7-Methoxybenzo(b)furan-2-yl)-3-methylisoxazole (2.04 g) obtained in Starting Material Synthesis Example 66 was dissolved in dichloromethane (30 ml) and boron tribromide (3 ml) was added dropwise with stirring at -40°C. The mixture was then stirred for 4 hr under ice-cooling and the reaction mixture was poured into ice water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give red crystals (1.96 g) of 5-(7-hydroxybenzo(b)furan-2-yl)-3-methylisoxazole. This compound and (S)-glycidyl nosylate (2.5 g) were dissolved in dimethylformamide (20 ml) and potassium carbonate (2.48 g) was added. The mixture was heated at 50°C for 3 hr. The reaction mixture was poured into ice water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily product (2.38 g). The oily product and 4-(naphthalen-2-yl)piperidine were dissolved in methanol (20 ml) and the solution was refluxed under heating for 1 hr.

After cooling, the solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (2.93 g) as an oil.

^{1}H-NMR(DMSO-d_6)δ: 1.93-2.25(m, 4H), 2.33(s, 3H), 2.75-3.35(m, 5H), 3.65(m, 2H), 4.27(m, 2H), 4.48(m, 1H), 5.00(bs, 1H), 6.91(s, 1H), 7.11(d, J=7.8, 1H), 7.27(t, J=7.8, 1H), 7.34(d, J=7.8, 1H), 7.45-7.54(m, 4H), 7.74(s, 1H), 7.88(m, 3H)

Example 50

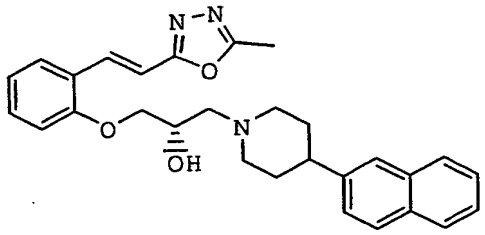
(S)-1-(2-(2-methylthiazol-4-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol



By the reactions in the same manner as in Starting Material Synthesis Example 5 using 4-(4-methoxybenzo(b)furan-2-yl)-2-methylthiazole (2.7 g) obtained in Starting Material Synthesis Example 67 and boron tribromide (7.5 g), 4-(4-hydroxybenzo(b)furan-2-yl)-2-methylthiazole (2.0 g) was obtained as yellow crystals. By the reactions in the same manner as in Starting Material Synthesis Example 2 using this compound, (S)-glycidyl nosylate (2.9 g) and potassium carbonate (3.1 g), (S)-4-(4-glycidyloxybenzo(b)furan-2-yl)-2-methylthiazole (2.1 g) was obtained as a brown oil. By the reactions in the same manner as in Example 1 using the brown oil and 4-(naphthalen-2-yl)piperidine (1.5 g), the title compound (0.3 g) was obtained as white crystals, melting point 148-150°C

Example 51

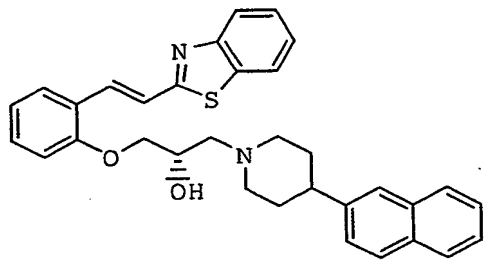
(S)-1-(2-(2-(5-methyl-1,3,4-oxadiazol-2-yl)vinyl)phenyloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol



To a solution (20 ml) of 2-(2'-hydroxystyryl)-5-methyl-1,3,4-oxadiazole (1.5 g) obtained in Starting Material Synthesis Example 68 in DMF was added potassium carbonate (2.0 g), and then (S)-glycidyl nosylate (1.9 g) was added. The mixture was stirred at 40°C for 3 hr. The reaction mixture was concentrated under reduced pressure and water was added. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oil (1.3 g). To the oil (1.3 g) was added methanol (50 ml), and then 4-(naphthalen-2-yl)piperidine (1.0 g) was added. The mixture was refluxed under heating for 3 hr. After concentration, the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (1.0 g) as white crystals, melting point 105-106°C.

Example 52

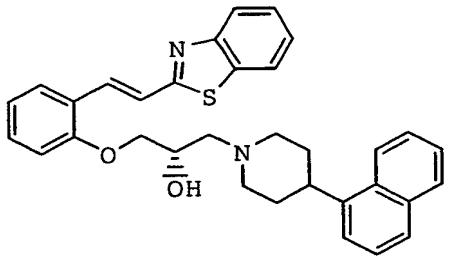
(S)-1-(2-(2-(benzothiazol-2-yl)vinyl)phenyloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol



To a solution (50 ml) of 2-(2'-hydroxystyryl)-benzothiazole (2.5 g) obtained in Starting Material Synthesis Example 69 in DMF was added potassium carbonate (5.0 g), and then (S)-glycidyl nosylate (2.4 g) was added. The mixture was stirred at 50°C for 2 hr. The reaction mixture was concentrated under reduced pressure and water was added. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give yellow crystals of (S)-2-(2'-glycidyloxy)styrylbenzothiazole (2.7 g). To the yellow crystals (1.5 g) was added methanol (50 ml), and then 4-(naphthalen-2-yl)piperidine (1.0 g) was added. The mixture was refluxed under heating for 3 hr. After concentration, the residue was purified by silica gel column chromatography (chloroform/methanol) to give white crystals (1.3 g), melting point 125-127°C.

Example 53

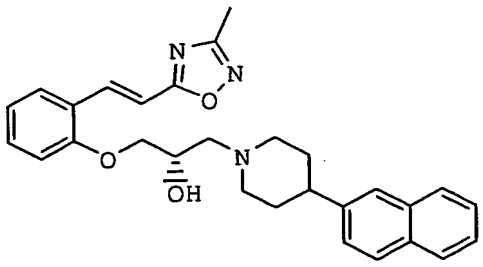
(S)-1-(2-(2-(benzothiazol-2-yl)vinyl)phenyloxy)-3-(4-(naphthalen-1-yl)piperidino)-2-propanol



By the reactions in the same manner as in Example 53 using (S)-2-(2'-glycidyloxystyryl)benzothiazole (0.9 g) and 4-(naphthalen-1-yl)piperidine (0.6 g), the title compound (0.98 g) was obtained as white crystals, melting point 146-148°C.

Example 54

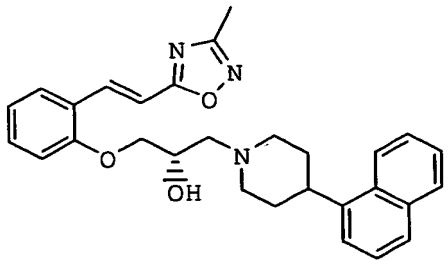
(S)-1-(2-(2-(3-methyl-1,2,4-oxadiazol-5-yl)vinyl)phenyloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol hydrochloride



To a solution (50 ml) of 5-(2'-hydroxystyryl)-3-methyl-1,2,4-oxadiazole (2.0 g) obtained in Starting Material Synthesis Example 70 in DMF was added potassium carbonate (3.0 g), and then (S)-glycidyl nosylate (2.6 g) was added. The mixture was stirred at 50°C for 2 hr. The reaction mixture was concentrated under reduced pressure and water was added. The mixture was extracted with ethyl acetate and the organic layer was dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure to give oily (S)-5-(2'-glycidyloxy)styryl-3-methyl-1,2,4-oxadiazole (2.2 g). This compound (1.2 g) was dissolved in methanol (50 ml), and 4-(naphthalen-2-yl)piperidine (1.0 g) was added. The mixture was refluxed under heating for 3 hr. After concentration, the concentrate was purified by silica gel column chromatography (chloroform/methanol), and 1 M solution of hydrochloric acid in methanol was added to the residue obtained. The precipitated crystals were collected by filtration and dried to give the title compound (1.2 g) as white crystals, melting point 184-186°C.

Example 55

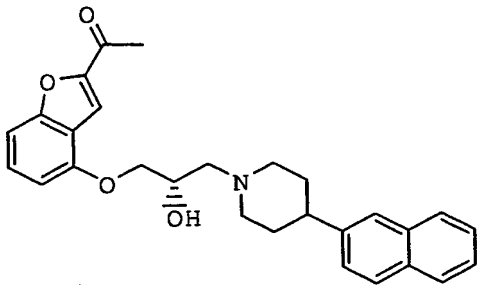
(S)-1-(2-(2-(3-methyl-1,2,4-oxadiazol-5-yl)vinyl)phenyloxy)-3-(4-(naphthalen-1-yl)piperidino)-2-propanol hydrochloride



By the reactions in the same manner as in Example 3 using 5-(2'-hydroxystyryl)-3-methyl-1,2,4-oxadiazole (1.0 g) obtained in Starting Material Synthesis Example 70 and 4-(naphthalen-1-yl)piperidine (1.0 g), the title compound (0.62 g) was obtained as white crystals, melting point 227-229°C (decomposition).

Example 56

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylmethylketone maleate

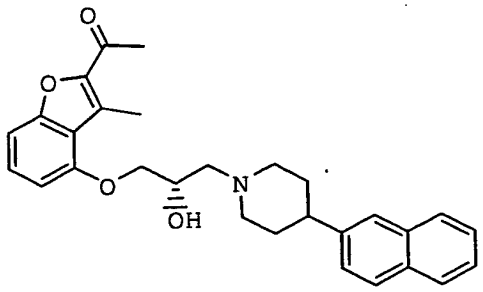


By the reactions in the same manner as in Example 3 using (S)-4-glycidyloxybenzo(b)furan-2-ylmethylketone (0.52 g) obtained in Starting Material Synthesis Example 71 and 4-(naphthalen-2-yl)piperidine (0.47 g), (S)-4-(2-hydroxy-3-(4-naphthalen-2-yl)piperidino)propyloxy)benzo(b)furan-2-ylmethylketone (0.87 g) was obtained as a brown oil. This was dissolved in ethyl acetate and maleic acid (0.22 g) was added. The precipitated crystals were recrystallized from a mixed solvent of isopropanol - ethyl acetate to give the title compound (0.76 g) as pale-yellow crystals, melting point 153-

155°C.

Example 57

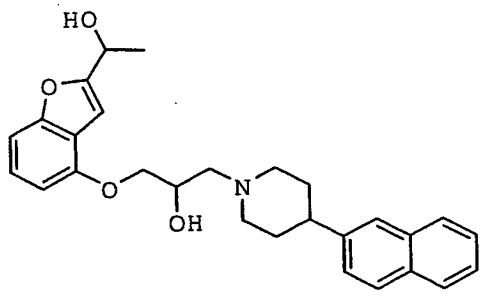
(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-3-methylbenzo(b)furan-2-ylmethylketone maleate



By the reactions in the same manner as in Example 3 using (S)-4-glycidyloxy-3-methylbenzo(b)furan-2-ylmethylketone (0.60 g) obtained in Starting Material Synthesis Example 72 and 4-(naphthalen-2-yl)piperidine (0.51 g), (S)-4-(2-hydroxy-3-(4-naphthalen-2-yl)piperidino)propyloxy)-3-methylbenzo(b)furan-2-ylmethylketone (1.1 g) was obtained as a brown oil. This was dissolved in ethyl acetate and maleic acid (0.25 g) was added. The precipitated crystals were recrystallized from a mixed solvent of isopropanol - ethyl acetate to give the title compound (0.82 g) as pale-yellow crystals, melting point 163-164°C.

Example 58

1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-yl)ethanol

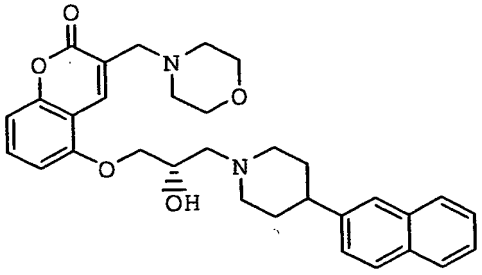


(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-ylmethylketone (0.30 g) obtained in

Example 56 was dissolved in methanol and sodium borohydride (30 mg) was added at room temperature. The mixture was stirred for 20 min. To the reaction mixture was added saturated aqueous ammonium chloride solution and the solvent was evaporated under reduced pressure. The obtained residue was dissolved in ethyl acetate, and the mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (0.24 g) as brown crystals, melting point 143-144°C.

Example 59

(S)-5-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-3-morpholinomethyl-2-chromenone

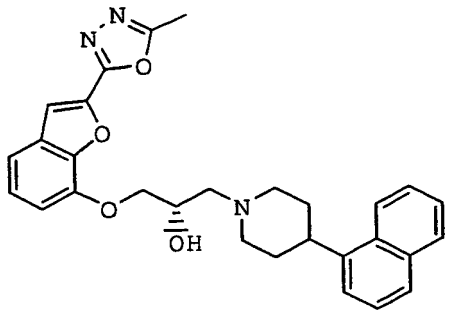


Red crystals (2 g) of 5-hydroxy-3-morpholinomethyl-2-chromenone and (S)-glycidyl nosylate (2 g) were dissolved in dimethylformamide (20 ml) and potassium carbonate (3 g) was added. The mixture was heated at 50°C for 5 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily product (1.10 g). The oily product and 4-(naphthalen-2-yl)piperidine were dissolved in methanol (20 ml) and the mixture was refluxed under heating for 3 hr. After cooling, the solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (0.63 g) as an oil.

^{1}H-NMR(DMSO-d_6)δ: 2.09-2.22(m, 4H), 2.58(m, 2H), 2.75-3.35(m, 5H), 3.64(m, 8H), 4.01(s, 2H), 4.15(m, 2H), 4.46(m, 1H), 5.00(bs, 1H), 6.99(m, 2H), 7.46-7.57(m, 4H), 7.75(s, 1H), 7.88(m, 3H), 8.31(s, 1H)

Example 60

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-7-yloxy)-2-(4-(naphthalen-1-yl)piperidino)ethanol



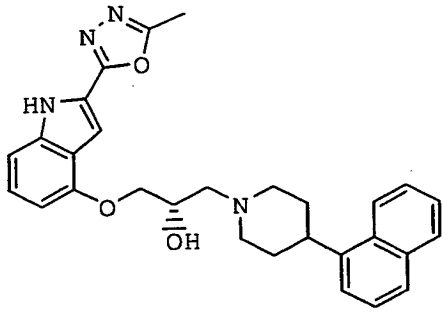
7-methoxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan (2 g) was dissolved in dichloromethane (50 ml) and boron tribromide (2 ml) was added dropwise with stirring at -8°C. The mixture was then stirred for 1 hr under ice-cooling and the reaction mixture was poured into ice water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give red crystals (1.5 g) of 7-hydroxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan. This compound and (S)-glycidyl nosylate (2 g) were dissolved in DMF (100 ml) and potassium carbonate (11 g) was added. The mixture was stirred at 50°C for 2 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily product (2 g). The oily product and 4-(naphthalen-1-yl)piperidine were dissolved in methanol (20 ml) and the mixture was refluxed under heating for 1 hr. After cooling, the solvent was concentrated under reduced pressure and the

residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (1.0 g) as a pale-yellow oil.

^{1}H-NMR(DMSO-d_6)δ: 1.77-1.83(m, 4H), 2.20-2.25(m, 2H), 2.47-2.66(m, 3H), 2.62(s, 3H), 3.04-3.13(m, 2H), 4.17(m, 2H), 4.30(m, 1H), 5.02(bs, 1H), 7.17(d, J=7.8, 1H), 7.32(t, J=7.8, 1H), 7.40(d, J=7.8, 1H), 7.50-7.58(m, 4H), 7.74(s, 1H), 7.81(d, J=7.8, 1H), 7.93(d, J=7.8, 1H), 8.23(d, J=7.8, 1H)

Example 61

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)indol-4-yloxymethyl)-2-(4-(naphthalen-1-yl)piperidino)ethanol



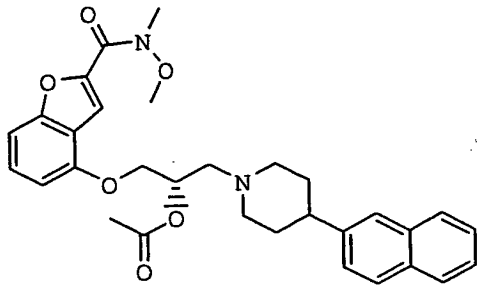
To a solution of 4-hydroxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)indole in dimethylformamide were added (S)-glycidyl nosylate (2 g) and potassium carbonate (2 g), and the mixture was heated at 50°C for 5 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol) to give yellow crystals (0.5 g). The yellow crystals and 4-(naphthalen-1-yl)piperidine were dissolved in methanol (10 ml) and the mixture was refluxed under heating for 2 hr. After cooling, the solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (0.36 g) as

yellow crystals, melting point 203-205°C.

^{1}H-NMR(DMSO-d_6)δ: 1.81-1.86(m, 4H), 2.33-2.39(m, 2H), 2.51-2.66(m, 3H), 2.58(s, 3H), 3.08-3.16(m, 2H), 4.05(m, 1H), 4.16(m, 2H), 4.92(bs, 1H), 6.58(d, J=7.8, 1H), 7.05(d, J=7.8, 1H), 7.13-7.19(m, 2H), 7.41-7.56(m, 4H), 7.75(d, J=7.8, 1H), 7.90(d, J=7.8, 1H), 8.14(d, J=7.8, 1H), 12.16(s, 1H)

Example 62

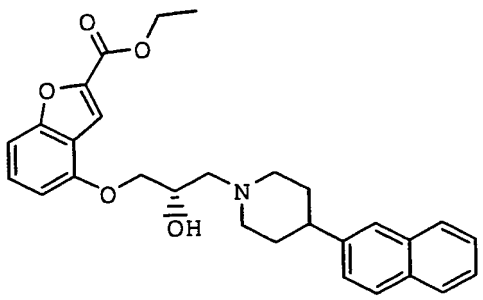
(S)-4-(2-acetoxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N-methoxy-N-methylbenzo(b)furan-2-carboxamide maleate



(S)-4-(2-Hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-N-methoxy-N-methylbenzo(b)furan-2-carboxamide (0.40 g) obtained in Example 6 was dissolved in pyridine (20 ml) and acetic anhydride (10 ml) was added at room temperature. The mixture was stood for one day. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give (S)-4-(2-acetoxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N-methoxy-N-methylbenzo(b)furan-2-carboxamide (0.34 g) as a brown oil. This was dissolved in ethanol and maleic acid (0.10 g) was added. The precipitated crystals were collected by filtration and dried to give the title compound (0.25 g) as pale-yellow crystals, melting point 125-127°C.

Example 63

ethyl (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)benzo(b)furan-2-carboxylate

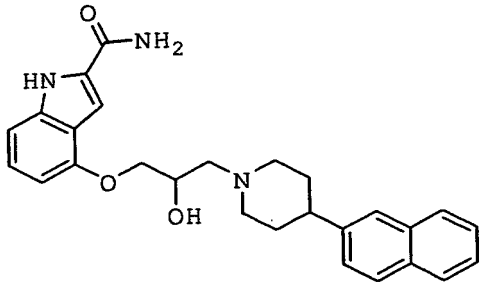


By the reactions in the same manner as in Example 1 using ethyl (S)-4-glycidyloxybenzo(b)furan-2-carboxylate (3.3 g) and 4-(naphthalen-2-yl)piperidine (2.7 g), the title compound (5.1 g) was obtained as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.42(t, J=7.3, 3H), 1.87-1.99(m, 4H), 2.20(t, J=3.1, 1H), 2.50-2.54(m, 1H), 2.63-2.74(m, 3H), 3.05(brd, J=10.7, 1H), 3.23(brd, J=11.2, 1H), 4.13-4.25(m, 3H), 4.45(q, J=7.3, 2H), 6.72(d, J=8.3, 1H), 7.21(d, J=8.3, 1H), 7.35-7.49(m, 4H), 7.67(s, 1H), 7.68(d, J=6.3, 1H), 7.81(d, J=8.3, 3H)

Example 64

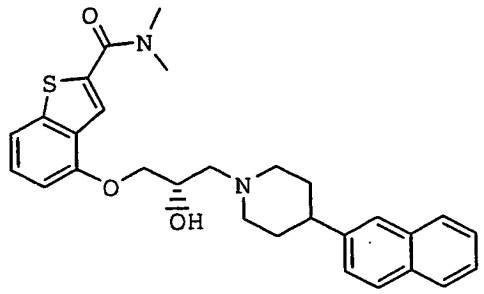
4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy) indole-2-carboxamide



By the reactions in the same manner as in Example 1 using 4-glycidyloxy-2-indole (1.8 g) and 4-(naphthalen-2-yl)piperidine (1.4 g), the title compound (1.8 g) was obtained as white crystals, melting point 200-202°C.

Example 65

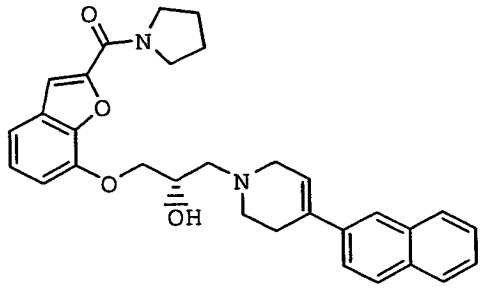
(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-N,N-dimethylbenzo(b)thiophene-2-carboxamide L-tartaric acid



By the reactions in the same manner as in Example 1 using 4-(glycidyloxy)benzo(b)thiophene-2-yl-N,N-dimethylcarboxamide (3.5 g) and 4-(naphthalen-2-yl)piperidine (2.0 g), an oil (2.5 g) was obtained. This was dissolved in a solution of L-tartaric acid (2.0 g) in ethanol. The precipitated crystals were collected by filtration and dried to give the title compound (1.4 g) as white crystals, melting point 173-175°C.

Example 66

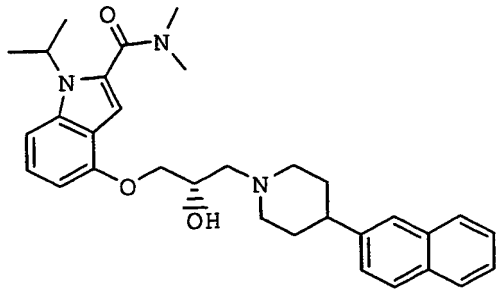
(S)-1-(7-(2-hydroxy-3-(3,6-dihydro-4-(naphthalen-2-yl)-2H-pyridin-1-yl)propyloxy)benzo(b)furan-2-ylcarbonyl)pyrrolidine



By the reactions in the same manner as in Example 1 using (S)-1-(7-glycidyloxybenzo(b)furan-2-ylcarbonyl)-pyrrolidine (2.1 g) and 3,6-dihydro-4-(naphthalen-2-yl)-2H-pyridine (1.8 g), the title compound (2.8 g) was obtained as white crystals, melting point 114-116°C.

Example 67

(S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)propyloxy)-1-isopropyl-N,N-dimethylindole-2-carboxamide

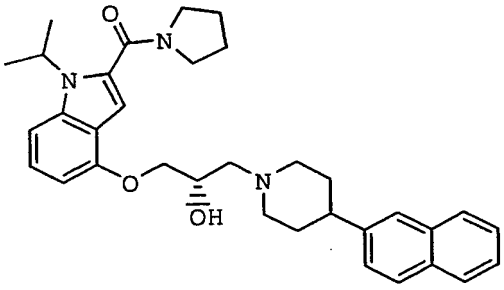


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-isopropylindole-2-carboxylic acid (2.5 g), dimethylamine hydrochloride (0.63 g), triethylamine (2.1 ml) and diethyl cyanophosphate (0.93 ml), the title compound (2.0 g) was obtained as a yellow oil.

^{1}H-NMR($CDCl_3$)δ: 1.62(d, J=6.8, 6H), 1.94-1.97(m, 4H), 2.24(t, J=3.1, 1H), 2.44-2.54(m, 1H), 2.61-2.76(m, 3H), 3.05(brd, J=10.7, 1H), 3.15(s, 6H), 3.23(brd, J=11.2, 1H), 4.13-4.29(m, 3H), 4.79(q, J=6.8, 1H), 6.54(d, J=6.8, 1H), 6.67(s, 1H), 7.13-7.15(m, 2H), 7.38-7.46(m, 3H), 7.66(s, 1H), 7.79(d, J=8.3, 3H)

Example 68

(S)-1-(4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-isopropylindole-2-carbonyl)pyrrolidine maleate

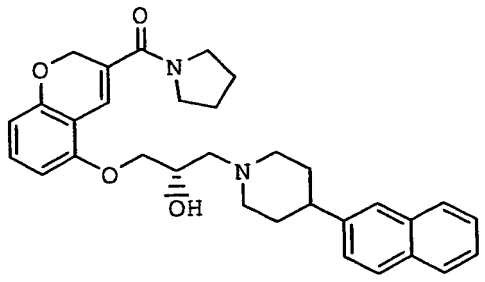


By the reactions in the same manner as in Example 3 using (S)-4-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidino)-propyloxy)-1-isopropylindole-2-carboxylic acid (2.5 g), pyrrolidine (0.44 g), triethylamine (2.1 ml) and diethyl cyanophosphate (0.93 ml), a brown oil (2.1 g) was obtained. This was dissolved in ethanol and maleic acid (0.4 g) was added.

The precipitated crystals were collected by filtration and dried to give the title compound (1.2 g) as pale-yellow crystals, melting point 154-155°C.

Example 69

(S)-1-(5-(2-hydroxy-3-(4-(naphthalen-2-yl)piperidin-1-yl)propyloxy)-chromen-3-ylcarbonyl)pyrrolidine



Red crystals (2.0 g) of 1-(5-hydroxychromen-3-ylcarbonyl)pyrrolidine and (S)-glycidyl nosylate (2.0 g) were dissolved in dimethylformamide (20 ml), and potassium carbonate (3 g) was added. The mixture was heated at 50°C for 3 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily product (3.27 g). The oily product and 4-(naphthalen-2-yl)piperidine were dissolved in methanol (20 ml) and the mixture was refluxed under heating for 3 hr. After cooling, the solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (0.12 g) as a brown oil.

^{1}H-NMR($CDCl_3$)δ: 1.91-2.02(m, 8H), 2.17(m, 2H), 2.48-2.70(m, 3H), 2.96(m, 1H), 3.15(m, 1H), 3.54(m, 4H), 3.73(bs, 1H), 4.00-4.13(m, 3H), 4.87(s, 2H), 6.47(d, J=7.8Hz, 1H), 6.50(d, J=7.8Hz, 1H), 7.11(t, J=7.8Hz, 1H), 7.16(s, 1H), 7.37(m, 3H), 7.64(s, 1H), 7.78(m, 3H)

By the same manner as in the above-mentioned Example,

the following compounds can be synthesized.

Example 70

(S)-1-(2-(5-methyloxazol-2-yl)-1H-indol-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

Example 71

(S)-1-(2-(5-methyloxazol-2-yl)-1H-indol-4-yloxy)-3-(4-(4-chlorophenyl)piperidino)-2-propanol

Example 72

(S)-1-(2-(5-methyloxazol-2-yl)-1H-indol-4-yloxy)-3-(4-(3,4-dichlorophenyl)piperidino)-2-propanol

Example 73

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indol-4-yloxy)-3-(4-(4-chlorophenyl)piperidino)-2-propanol

Example 74

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indol-4-yloxy)-3-(4-(3,4-dichlorophenyl)piperidino)-2-propanol

Example 75

(S)-1-(2-(4-methyl-1H-imidazol-2-yl)-1H-indol-4-yloxy)-3-(4-(3,4-dichlorophenyl)piperidino)-2-propanol

Example 76

(S)-1-(2-(5-methyl-1H-pyrazol-3-yl)-1H-indol-4-yloxy)-3-(4-(3,4-dichlorophenyl)piperidino)-2-propanol

Example 77

(S)-1-(2-(3-methylisoxazol-5-yl)-1H-indol-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

Example 78

(S)-1-(2-(5-methyloxazol-2-yl)-1H-indol-4-yloxy)-3-(4-(4-methylphenyl)piperidino)-2-propanol

Example 79

(R)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indol-4-yloxy)-3-(4-(4-methylphenyl) piperidino)-2-propanol

Example 80

(S)-1-(2-(5-methyloxazol-2-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

Example 81

(S)-3-(4-(3,4-dichlorophenyl)piperidino)-1-(2-(5-methyloxazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol dihydrochloride

4-hydroxy-2-(5-methyl-1,3-oxazol-2-yl)benzo(b)furan (11.0 g) and (S)-glycidyl nosylate (13.0 g) were dissolved in dimethylformamide (100 ml) and potassium carbonate (15.0 g) was added. The mixture was stirred at room temperature for 10 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oil (10.0 g). The oil and 4-(3,4-dichlorophenyl)piperidine were dissolved in methanol (100 ml) and the mixture was refluxed under heating for 2 hr. After cooling, the solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform/methanol). The obtained yellow oil (10 g) was dissolved in acetone and hydrochloric acid was added to give a hydrochloride. Recrystallization from ethanol gave the title compound (7.0 g) as pale-yellow crystals, melting point 190°C (decomposition).

^{1}H-NMR(DMSO-d_6)δ: 2.02-2.24(m, 4H), 2.43(s, 3H), 2.92(m, 1H), 3.20(m, 2H), 3.35-3.48(m, 2H), 3.71-3.81(m, 2H), 4.13-4.23(m, 2H), 4.57(m, 1H), 6.89(d, J=7.8, 1H), 7.08(s, 1H), 7.26-7.31(m, 2H), 7.37(t, J=7.8, 1H), 7.50(s, 1H), 7.56-7.67(m, 2H), 10.37(bs, 1H)

Example 82

(S)-1-(2-(5-methyloxazol-2-yl)benzo(b)furan-4-yloxy)-3-(4-(4-chlorophenyl)piperidino)-2-propanol

Example 83

(S)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-3-(4-(4-chlorophenyl)piperidino)-2-propanol

Example 84

(R)-1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-

3-(4-(naphthalen-2-yl)piperidino)-2-propanol

Example 85

(S)-1-(2-(3-methylisoxazol-5-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

Example 86

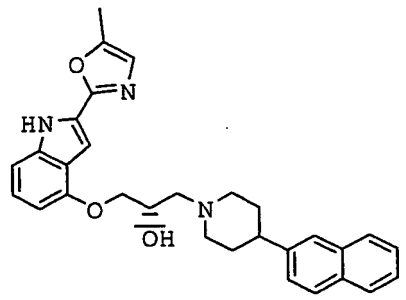
(S)-1-(2-(5-methylthiazol-2-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

Example 87

(S)-1-(2-(5-methylthiazol-2-yl)-1H-indol-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol

The structural formulas of the compounds of Examples 70 to 87 are shown in the following.

70



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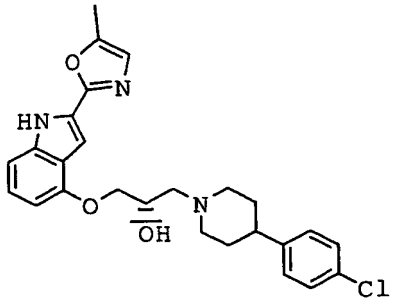

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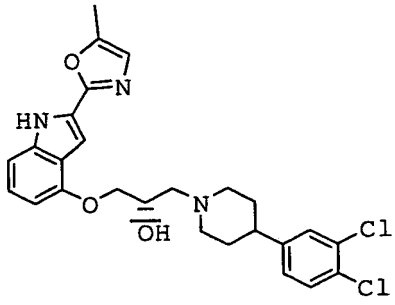

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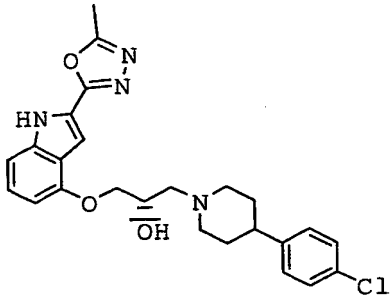

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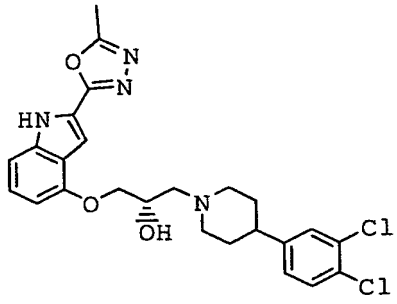

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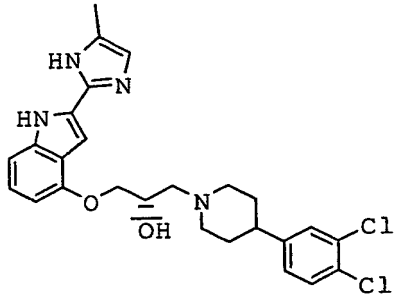

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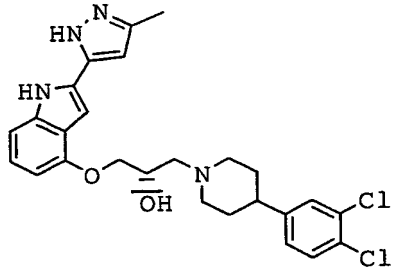

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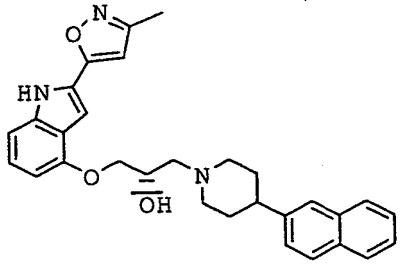

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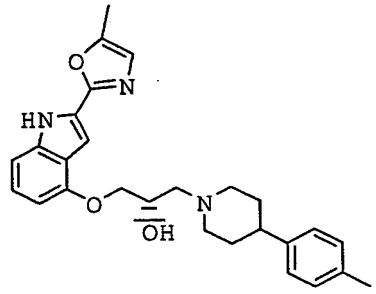

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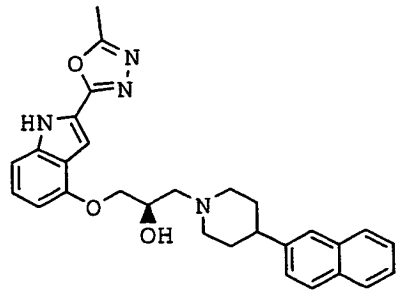

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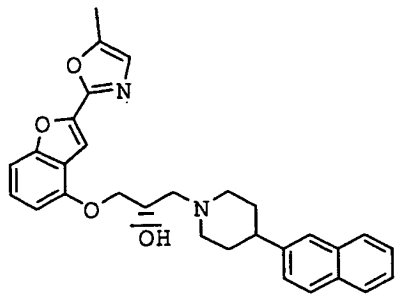

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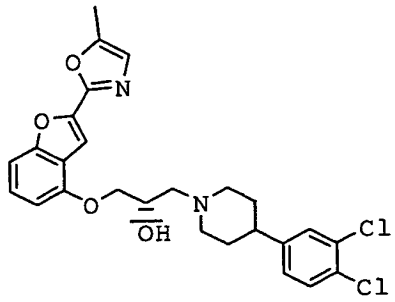

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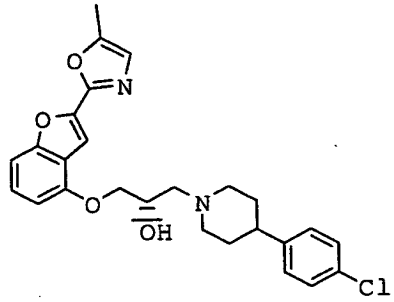

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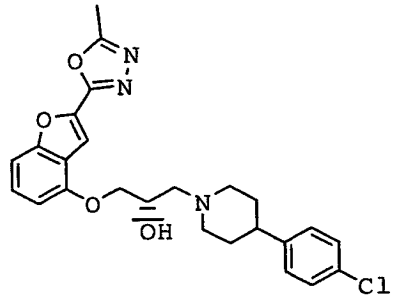

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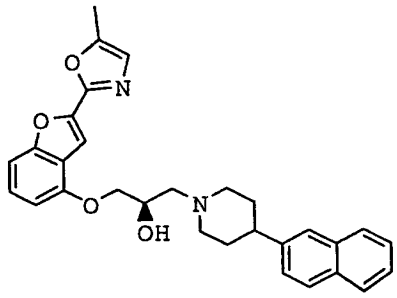

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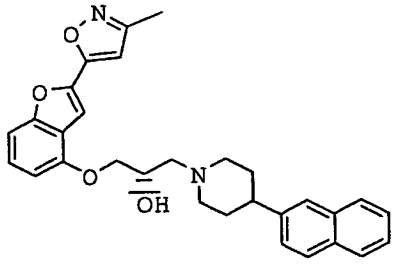

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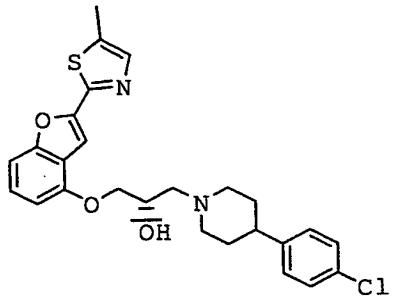

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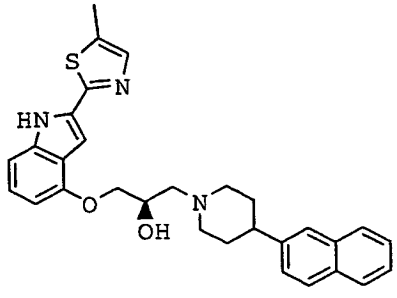
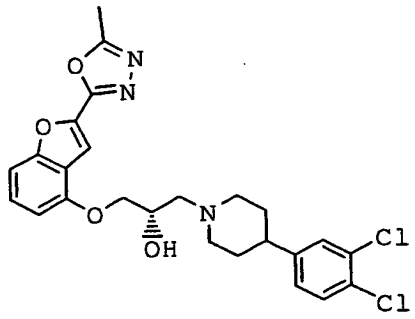


Example 88

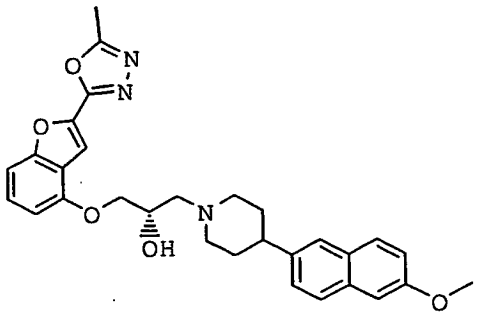
(S)-1-(4-(3,4-dichlorophenyl)piperidino)-3-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol hydrochloride 1/4hydrate



By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole (23.0 g) obtained in the same manner as in Starting Material Synthesis Example 39 and 4-(3,4-dichlorophenyl)-piperidine (18.6 g), a brown oil (39.0 g) was obtained. This was dissolved in ethanol. A solution of hydrochloric acid in ether was added and the mixture was allowed to stand. The precipitated crystals were collected by filtration and dried to give the title compound (23.5 g) as pale-yellow crystals, melting point 126-128°C.

Example 89

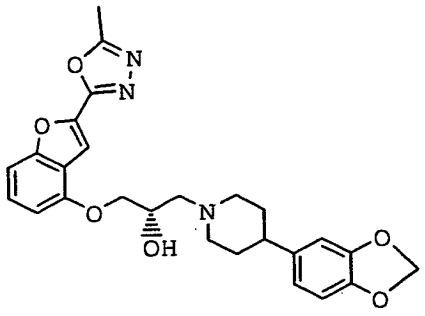
(S)-1-(4-(6-methoxynaphthalen-2-yl)piperidino)-3-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol



By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole (1.4 g) obtained in Starting Material Synthesis Example 39 and 4-(6-methoxynaphthalen-2-yl)piperidine (1.2 g), crude crystals were obtained. This was recrystallized from ethyl acetate to give the title compound (1.2 g) as white crystals, melting point 156-158°C.

Example 90

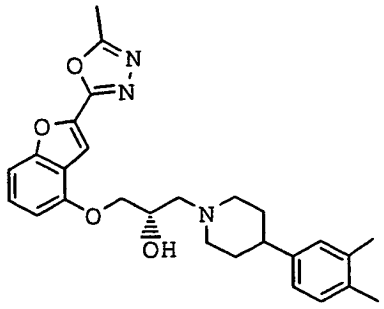
(S)-1-(4-(3,4-methylenedioxyphenyl)piperidino)-3-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol hydrochloride monohydrate



By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole (0.50 g) obtained in Starting Material Synthesis Example 39 and 4-(3,4-methylenedioxyphenyl)piperidine (0.36 g), a brown oil (0.42 g) was obtained. This was dissolved in acetone and a solution of hydrochloric acid in ether was added. The solvent was concentrated under reduced pressure and the resulting crude crystals were recrystallized from a mixed solvent of isopropanol - ethyl acetate (2:1) to give the title compound (0.27 g) as pale-yellow crystals, melting point 200-202°C.

Example 91

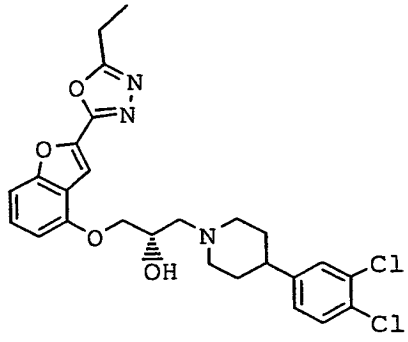
(S)-1-(4-(3,4-dimethylphenyl)piperidino)-3-(2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol hydrochloride monohydrate



By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-oxadiazole (0.50 g) obtained in Starting Material Synthesis Example 39 and 4-(3,4-dimethylphenyl)piperidine (0.33 g), a brown oil (0.64 g) was obtained. This was dissolved in acetone and a solution of hydrochloric acid in ether was added. The solvent was concentrated under reduced pressure and the resulting crude crystals were recrystallized from a mixed solvent of isopropanol - isopropyl ether (2:1) to give the title compound (0.33 g) as pale-yellow crystals, melting point 150-152°C.

Example 92

(S)-3-(4-(3,4-dichlorophenyl)piperidino)-1-(2-(5-ethyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol hydrochloride 1/2 hydrate

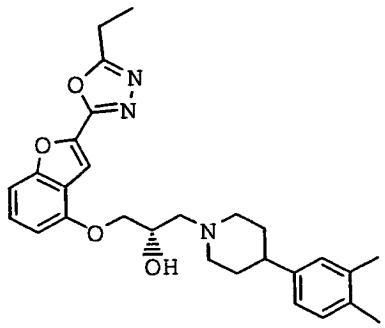


The yellow oil (0.90 g) obtained by the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo-(b)furan-2-yl)-5-ethyl-1,3,4-oxadiazole (0.50 g) obtained in

Starting Material Synthesis Example 76 and 4-(3,4-dichlorophenyl)piperidine (0.40 g) was dissolved in acetone and a solution of hydrochloric acid in ether was added to give a hydrochloride. Recrystallization from a mixed solvent of isopropanol - isopropyl ether gave the title compound (0.34 g) as white crystals, melting point 148-150°C.

Example 93

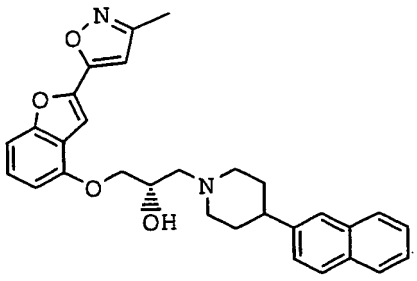
(S)-3-(4-(3,4-dimethylphenyl)piperidino)-1-(2-(5-ethyl-1,3,4-oxadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol hydrochloride 1/2 hydrate



A yellow oil (5.0 g) obtained by the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo-(b)furan-2-yl)-5-ethyl-1,3,4-oxadiazole (3.0 g) obtained in Starting Material Synthesis Example 76 and 4-(3,4-dimethylphenyl)piperidine (2.0 g) was dissolved in acetone - ethyl acetate, and a solution of hydrochloric acid in ether was added to give a hydrochloride. Recrystallization from a mixed solvent of acetone - ethyl acetate gave the title compound (2.0 g) as pale-yellow crystals, melting point 178-180°C.

Example 94

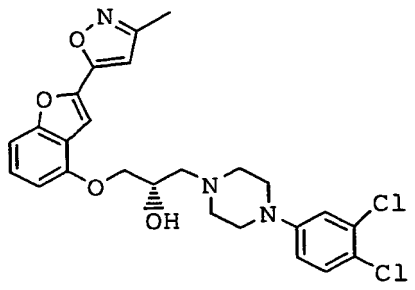
(S)-1-(2-(3-methylisoxazol-5-yl)benzo(b)furan-4-yloxy)-3-(4-(naphthalen-2-yl)piperidino)-2-propanol hydrochloride 1/4 hydrate



By the reactions in the same manner as in Example 1 using (S)-5-(4-glycidyloxybenzo(b)furan-2-yl)-3-methylisoxazole (0.50 g) obtained in Starting Material Synthesis Example 79 and 4-(naphthalen-2-yl)piperidine (0.37 g), a brown oil (0.69 g) was obtained. This was dissolved in ethyl acetate and a solution of hydrochloric acid in ether was added. The precipitated crystals were collected by filtration and dried to give the title compound (0.36 g) as white crystals, melting point 152-154°C.

Example 95

(S)-1-(4-(3,4-dichlorophenyl)piperazin-1-yl)-3-(2-(3-methylisoxazol-5-yl)benzo(b)furan-4-yloxy)-2-propanol hydrochloride 1/4 hydrate

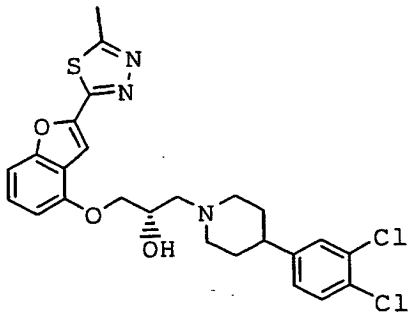


By the reactions in the same manner as in Example 1 using (S)-5-(4-glycidyloxybenzo(b)furan-2-yl)-3-methylisoxazole (0.50 g) obtained in Starting Material Synthesis Example 79 and 4-(3,4-dichlorophenyl)piperazine (0.40 g), a brown oil (0.60 g) was obtained. This was dissolved in isopropanol and a solution of hydrochloric acid in ether was added. The precipitated crystals were collected by filtration and dried to give the

title compound (0.36 g) as brown crystals, melting point 250°C or higher.

Example 96

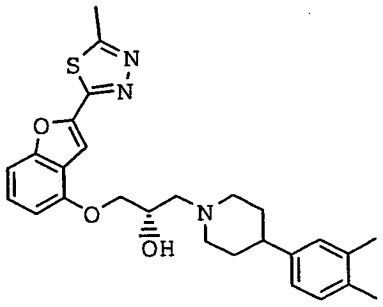
(S)-1-(4-(3,4-dichlorophenyl)piperidino)-3-(2-(5-methyl-1,3,4-thiadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol hydrochloride monohydrate



By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-thiadiazole (0.35 g) obtained in Starting Material Synthesis Example 82 and 4-(3,4-dichlorophenyl)piperidine (0.28 g), a brown oil (0.60 g) was obtained. This was dissolved in isopropanol and a solution of hydrochloric acid in ether was added. The precipitated crystals were collected by filtration and dried to give the title compound (0.19 g) as pale-yellow crystals, melting point 220-222°C.

Example 97

(S)-1-(4-(3,4-dimethylphenyl)piperidino)-3-(2-(5-methyl-1,3,4-thiadiazol-2-yl)benzo(b)furan-4-yloxy)-2-propanol hydrochloride monohydrate



By the reactions in the same manner as in Example 1 using (S)-2-(4-glycidyloxybenzo(b)furan-2-yl)-5-methyl-1,3,4-thiadiazole (0.35 g) obtained in Starting Material Synthesis Example 82 and 4-(3,4-dimethylphenyl)piperidine (0.32 g), a brown oil (0.50 g) was obtained. This was dissolved in isopropanol and a solution of hydrochloric acid in ether was added. The precipitated crystals were collected by filtration and dried to give the title compound (0.21 g) as pale-yellow crystals, melting point 191-194°C.

Formulation Example 1

Of the compounds of the present invention, a compound of the formula (I) (50 mg) is thoroughly kneaded with lactose (98 mg), cornstarch (45 mg) and hydroxypropylcellulose (3 mg) in a kneader. The kneaded product is passed through a 200 mesh sieve, dried at 50°C and passed through a 24 mesh sieve. The resulting product is mixed with talc (3 mg) and magnesium stearate (1 mg) and compressed with a 9 mm diameter pounder to give a tablet weighing 200 mg. The tablets may be sugar coated or film coated as necessary.

Experimental Example 1: 5-HT_{1A} receptor binding test

The experiment was conducted according to the method of M.D. Hall et al (J. Neurochem. 44, 1685-1696 (1985)).

Cryopreserved rat hippocampus was homogenized in a 20-fold wet weight amount of 50 mM Tris-HCl buffer (pH 7.4), and the homogenate was centrifuged at 500xg for 10 min. The supernatant was centrifuged at 40000xg for 10 min and the sediment was incubated at 37°C for 10 min, which was followed by centrifugation at 40000xg for 10 min. To the sediment was added a 20-fold amount of 50 mM Tris-HCl buffer (pH 7.4) and the mixture was homogenized, which was followed by centrifugation again at 40000xg for 10 min. 50 mM Tris-HCl buffer (pH 7.4, 100-fold volume) containing 1 mM $MnCl_2$ was

added to the sediment and the mixture was homogenized, which was used as a membrane solution. To a 96 well plate were successively added a test solution (25 ml), (^{3}H)-8-OH-DPAT solution (final concentration 2 nM, 25 ml) and the membrane solution (0.45 ml) preincubated at 37°C, and incubated at 37°C for 12 min. After completion, the reaction mixture was filtered through a GF/B glass filter and the filter was washed 5 times with 50 mM Tris-HCl buffer (pH 7.4). The radioactivity left on the filter was measured with a Top Count. For total binding measurement, 0.005N hydrochloric acid (25 ml) was used, and for the measurement of nonspecific binding, a test solution containing WAY-100635 (final concentration 1M, 25 ml) instead of the test substance was used. The total binding and nonspecific binding were measured in quadruplicate, and the test substance was measured in duplicate.

The IC_{50} value was calculated by two-point interpolation and Ki value was calculated according to the following equation using Kd value obtained from each measurement.

$Ki=IC_{50}/(1+C/Kd)$

IC_{50}: concentration of 50% binding inhibition

C: concentration of ligand

Experimental Example 2: 5-HT transporter binding test

The experiment was conducted according to the method of Habert, E. et al (Eur. J. Pharmacol., 118; 107-114 (1985)).

Rat brain cortex was homogenized using Polytron in ice-cooled 50 mmol/L Tris-HCl buffer (pH 7.4). After centrifugation at 1000×g and 4°C for 10 min, the supernatant was transferred to a different centrifugation tube. This was centrifuged at 40000×g and 4°C for 20 min, and 50 mmol/L Tris-HCl buffer (pH 7.4) was added to the sediment to give a suspension. This was incubated at 37°C for 10 min, centrifuged at 40000×g and 4°C for 20 min, and suspended in 50 mmol/L Tris-HCl buffer (pH 7.4) (diluted 100-fold of brain wet weight) containing 120 mmol/L NaCl and 5 mmol/L KCl, which was used as

a membrane solution. For binding inhibition test, it was reacted with (^{3}H) paroxetine prepared to the final concentration of 0.2 nmol/L in a plastic test tube at 25°C for 90 min. For total binding, a solvent was used and for nonspecific binding, fluvoxamine having a final concentration of 10 μmol/L was used. Using a cell harvester, the reaction mixture was filtered through a GF/B glass filter treated with 0.1% polyethyleneimine to stop the reaction and washed 3 times with 3 mL of ice-cooled 50 mmol/L Tris-HCl buffer (pH 7.4). The radioactivity was measured using a β plate.

The results of Experimental examples 1 and 2 indicated that the Ki values of the inventive compounds for 5-HT_{1A} receptor binding test and 5-HT transporter binding test were not more than 0.1 to 100 nM.

Experimental Example 3: antagonistic action against lowering of body temperature

From the antagonistic action of the test substance against decrease in the body temperature due to 8-OH-DPAT, transfer of the test substance into the brain was established. At the same time, it was clarified if the test substance acts as an agonist or as an antagonist on the 5-HT_{1A} receptor.

The rectal temperature of male ddY mice was measured with a digital thermostat (KN-91, Natsume) (pre-value). Thereafter, the test substance was administered orally or parenterally, and after a certain time, 8-OH-DPAT (1 mg/kg) was subcutaneously administered. The rectal temperature was measured 30 min later (post-value).

The results of Experimental Example 3 establish that the compound of the present invention is an antagonist on 5-HT_{1A} receptor, because the compound given orally in 0.1 - 100 mg/kg antagonizes the lowering of the body temperature due to 8-OH-DPAT. From the results, it is suggested that the compound of the present invention is superior in the bioavailability and transfer into the brain.

Experimental Example 4: forced swimming test

The test substance was administered orally or parenterally to male ddY mice, and after a certain time, the mice were placed in a water tank (material: vinyl chloride, color: black, inner diameter: 10 cm, height: 25 cm, water depth: 15 cm, water temperature: 25°C), and subjected to 6 min test trial. The movement of the animal was videotaped with a CCD camera set right above the water tank, and analyzed against immobility time during 4 minutes from 2 to 6 min after the start of swimming, using an image analysis system/forced swimming analysis program [Neuroscience Inc.: Videoimage motion analyzer (AXIS series)/(TARGET/7M)].

The results of Experimental Example 4 reveal that, while the conventional SSRI requires several days for expression of an action, the compound of the present invention significantly shortened the immobility time by the single oral administration of 0.1 - 100 mg/kg thereof. From this, it is suggested that the compound of the present invention can be a so-called rapid onset antidepressant that shows quick expression of the anti-depressive effect, as compared to conventional SSRI.

【Effect of the Invention】

The compound of the present invention is useful as what is called a rapid onset antidepressant that shows quick expression of an anti-depressive effect. It is also useful for the treatment of 5-HT mediated diseases of the central nervous system, such as schizophrenia, anxiety neurosis, obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder(social phobia), seasonal emotional disorder (seasonal affective disorder), Anorexia Nervosa, Bulimia Nervosa, nocturnal enuresis, children's hyperlocomotion, post-traumatic stress disorder (PTSD), senile dementia, hemicrania, stroke, Alzheimer's disease, recognition disorder, hypertension, gastrointestinal injury, feeding disorders, abnormal body temperature regulation and sexual disorder, pain, abnormality

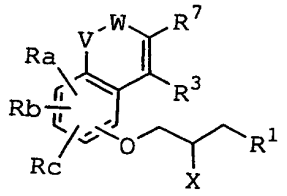
in the cardiovascular system, drug abuse and the like.

【Document】 Abstract

【Summary】

【Problem】 This present invention aims at providing antidepressants and the like, which simultaneously have high affinity for 5-HT_{1A} receptor and 5-HT reuptake inhibitory activity, and which are quick in expressing an anti-depressive effect.

【Solving Means】 A compound of the formula



(I)

wherein each symbol is as defined in the specification, an optically active compound thereof, a pharmaceutically acceptable salt thereof and hydrates thereof.

【Main Drawing】 None